Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2006-15

Sulfuryl Fluoride

The active ingredient sulfuryl fluoride and associated end-use product ProFume Gas Fumigant, containing 99.8% sulfuryl fluoride, for the control of stored product pests such as Indian meal moth, confused flour beetle, saw-toothed grain beetle, warehouse beetle and granary weevil in empty cereal grain mills, associated empty storage facilities and empty food processing plants have been granted temporary registration under the Pest Control Products Regulations.

This Regulatory Note provides a summary of data reviewed and the rationale for the regulatory decision for these products.

(publié aussi en français)

20 December 2006

This document is published by the Alternative Strategies and Regulatory Affairs Division, Pest Management Regulatory Agency. For further information, please contact:

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ISBN: 978-0-662-44700-9 (978-0-662-44701-6)
Catalogue number: H113-7/2006-15E (H113-7/2006-15E-PDF)

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has carried out an assessment of available information in accordance with the Pest Control Products Regulations and has found it sufficient to allow a determination of the safety, merit and value of sulfuryl fluoride and the associated end-use product ProFume Gas Fumigant. The Agency has concluded that the use of sulfuryl fluoride and the end-use product ProFume Gas Fumigant in accordance with the label has merit and value consistent with the Regulations and does not entail an unacceptable risk of harm. Therefore, based on the considerations outlined above, the use of sulfuryl fluoride and the end-use product ProFume Gas Fumigant for the control of of stored product pests such as Indian meal moth, confused flour beetle, saw-toothed grain beetle, warehouse beetle and granary weevil in empty cereal grain mills, associated empty storage facilities and empty food processing plants have been granted temporary registration pursuant to the Regulations.

Methods for analysing sulfuryl fluoride in air are available to research and monitoring agencies upon request to the PMRA.

Dow AgroSciences Canada Inc. will be carrying out additional ambient air monitoring studies, and possibly atmospheric transformation studies, as a condition of this temporary registration. Following the review of this information, the PMRA will publish a proposed regulatory decision document and request comments from interested parties before proceeding with a final regulatory decision.

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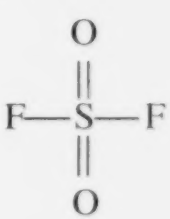
1.0 The Active Substance, its Properties and Uses

1.1 Identity of the Active Substance and Impurities

Identification of the Technical Grade Active Ingredient

Active substance		Sulfuryl fluoride
Function		Fumigant
Chemical name		
1.	International Union of Pure and Applied Chemistry	Sulfuryl fluoride
2.	Chemical Abstracts Service (CAS)	Sulfuryl fluoride
CAS number		2699-79-8
Molecular formula		F_2O_2S
Molecular weight		102.06
Structural formula		
Nominal purity of active ingredient		99.8% nominal (limits: 99.4–100%)
Identity of relevant impurities of toxicological, environmental or other significance		The technical grade sulfuryl fluoride does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances

1.2 Physical and Chemical Properties of Active Substances and End-use Product(s)

Technical Product: Sulfuryl Fluoride Technical

Property	Result	Comment
Colour and physical state	Colourless gas	
Odour	Not determined due to hazardous nature of test substance.	
Melting point or range	-136.7°C at 760 mmHg	
Boiling point or range	-54°C at 760 mmHg	
Density	1.32 at 25°C	
Vapour pressure at 20°C	1.6×10^6 Pa	
Henry's law constant at 20°C	1.1–1.5	Rapid loss from a water surface or moist soil (USEPA 1975a)
Ultraviolet (UV) – visible spectrum	**Solvent** / **λ max (nm)** Water / 277 Acidic / 278 Basic / No absorption, hydrolized in aqueous alkali Not expected to absorb UV at > 300 nm.	
Solubility in water at 20°C	1.04 g/L	
Solubility in organic solvents	**Solvent** / **Solubility (g/L)** Methanol / 33.3 Acetone / 71 Xylene / 25 1,2-dichloroethane / 25 Ethyl acetate / 59 *n*-Heptane / 22 *n*-Octanol / 14	

Property	Result	Comment
n-Octanol–water partition coefficient (K_{ow})	$\log K_{ow} = 0.14$	
Dissociation constant (pK_a)	Not applicable. The product is a gas and does not dissociate.	
Stability (temperature, metal)	Stable to heat normally encountered in structural and other fumigations. Temperatures over 260°C will cause decomposition products which can be corrosive and can etch glass. Sulfuryl fluoride is unreactive. Hydrolysis is slow in water but rapid in basic solutions.	

End-use Product: ProFume Gas Fumigant

Property	Result
Colour	Colourless
Odour	Not determined due to hazardous nature of test substance.
Physical state	Gas at 20°C
Formulation type	Pressurized product
Guarantee	99.8% nominal (limits: 99.4–100%)
Formulants	The product does not contain any USEPA List 1 formulants or formulants known to be TSMP Track 1 substances.
Container material and description	Gas cylinder
Specific gravity	1.32 at 25°C
pH of 1% dispersion in water	Not applicable. The product is a gas.
Oxidizing or reducing action	A mild oxidant
Storage stability	Stable for at least one year at ambient temperature.
Explodability	The product does not have explosive properties.

1.3 Details of Uses

Dow AgroSciences Canada Inc. has submitted an application to register ProFume Gas Fumigant (99.8% sulfuryl fluoride) for use in empty cereal grain mills, empty storage facilities and empty food processing facilities for the control of stored product pests such as Indian meal moth, confused flour beetle, saw-toothed grain beetle, warehouse beetle and granary weevil. The proposed product is to be applied by licensed applicators using the ProFume Fumiguide computer program, which identifies the parameters under which the fumigation can take place (e.g., maximum dose and concentration, minimum length of fumigation and temperatures).

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Substance as Manufactured

A gas chromatography method was provided for the simultaneous determination of the active substance and its impurities. Detection is by thermal conductivity, and quantitation by external calibration using external standards. The method for the determination of the active ingredient was shown to be precise with a relative standard deviation of 0.3%, accurate by a mean percent recovery of 99.1% and specific as demonstrated by the absence of interferences at the retention time of the analyte.

2.2 Method for Formulation Analysis

The method for formulation analysis is the same as for analysis of the active substance, described in Section 2.1.

2.3 Methods for Residue Analysis

2.3.1 Methods for Environmental Residue Analysis

Analytical methodologies for the analysis of residues in soil, sediment and water were not provided. Sulfuryl fluoride in air samples was determined using a fluoride specific electrode. The method involves the extraction of the analyte from charcoal adsorbent tubes that are used to trap the sulfuryl fluoride. The charcoal from the tubes was desorbed using sodium hydroxide, and the extract, heated to convert sulfuryl fluoride to fluoride and sulfate. The fluoride content is measured using a fluoride selective electrode and quantitated using the single known standard addition. Due to fluoride interference, the fluoride found from the blank sample was subtracted from the treated samples to obtain accurate recovery. The recovery of the method ranged from 74% to 100% with a mean recovery of 86% for 14 determinations. The precision of the method was expressed by the relative standard deviation of 8.0%. The limit of quantitation (LOQ) of the method was established at 0.035 ppm. Based on the validation data provided, the method is assessed to be accurate and precise for use as a postregistration monitoring method.

2.3.2 Multiresidue Methods for Residue Analysis

Not provided.

2.3.3 Methods for Residue Analysis of Plants and Plant Products

Not provided.

2.3.4 Methods for Residue Analysis of Food of Animal Origin

Not applicable as no food uses were evaluated.

3.0 Impact on Human and Animal Health

3.1 Integrated Toxicological Summary

A detailed review of the toxicological database for sulfuryl fluoride was conducted. The database is considered adequate to define most of the effects that may result from exposure to this chemical. The majority of the toxicity studies were conducted via the inhalation route of exposure.

Absorption and excretion of sulfuryl fluoride was very rapid following inhalation, with the urine being the primary route of excretion (86–96% of the total radioactivity excreted). Results from this study indicated that approximately 12–18% of the inhaled dose was absorbed; however, limitations of the study lead to uncertainty with respect to the validity of this estimation. The lungs, the respiratory and olfactory turbinates, the kidneys and the spleen contained the highest levels of radioactivity, with small amounts of radioactivity distributed evenly among all tissues seven days postexposure, suggesting incorporation of radiolabelled sulfur atom into proteins. Sulfuryl fluoride is metabolized by hydrolysis to fluorosulfate and sulfate following sequential loss of two fluorine atoms.

Sulfuryl fluoride is considered of high toxicity by the oral and inhalation routes as well as of low toxicity by the dermal route. Once pressurized, liquid sulfuryl fluoride causes cryogenic burns on contact with skin and eyes. Sulfuryl fluoride is not considered to be a dermal sensitizer. This acute toxicity profile also applies to the end-use product, ProFume Gas Fumigant, containing 99.8% sulfuryl fluoride.

Clinical signs of toxicity in the form of tremors, lethargy, incapacitation, convulsions, tetany and impaired respiratory function were noted following inhalation exposures ranging from a single 4-hour exposure to daily 6-hour exposures over 13 weeks.

Following repeated inhalation exposures as short as two weeks, sulfuryl fluoride appeared to target the brain, respiratory system and kidney in the rat, rabbit, mouse and dog. The incidence and severity of brain lesions appeared to increase with exposure level, and the dose at which effects were observed generally decreased with increasing duration of exposure. Effects on the

teeth in the form of dental fluorosis and dental abnormalities were also noted, but only in rats and dogs after longer exposure durations (13 weeks to 1 year). At high exposure levels, sulfuryl fluoride resulted in mortality in all species examined. Effects on the heart (inflammation of the epicardium) and endocrine organs (hypertrophy of the adrenal cortex, thyroid cyst, hypertrophy of epithelial cells of the thyroid gland) were noted only at the high concentrations that caused mortality in the 2-week rat and rabbit studies, the 1-year dog study, the 18-month mouse study and the 2-year rat study. These findings are not likely indicative of a target organ effect on the heart and endocrine system as they only appeared when the health of the animals was already severely compromised.

In two-week range-finding studies, inflammation of the respiratory tract was noted at the lowest dose that caused adverse effects in rabbits and at higher exposure levels in the rat and dog. Renal effects, including hyperplasia of the collecting ducts, basophilia in proximal tubules, and increased kidney weight, were observed in the rat and mouse at the lowest concentrations causing adverse findings. Vacuolation of the brain occurred in the mouse and rabbit, but was not observed in rats or dogs, following two weeks of exposure to sulfuryl fluoride.

In 13-week inhalation toxicity studies, vacuolation of the brain was noted in the rabbit, mouse and dog at the study lowest observed adverse effect levels (LOAELs) and in the rat at higher exposure levels. Malacia (necrosis), a more severe brain lesion, was observed in rabbits and dogs only. The rabbit had the lowest LOAEL for brain lesions in the 13-week inhalation toxicity studies. Dental fluorosis was observed in rats at the study LOAEL. The rat also showed clinical (elevated urea nitrogen, decreased urinary specific gravity) and pathological (hyperplasia of the renal collecting ducts, decreased protein droplet formation in the renal cortex) signs of renal toxicity as well as effects on the respiratory tract (lung foci, inflammation of the nasal mucosa and the trachea, alveolar histiocytosis). Respiratory tract lesions (degeneration of the nasal olfactory epithelium, hypertrophy and hyperplasia of the respiratory epithelium of the nasal passages) were also noted in the rabbit following exposure to sulfuryl fluoride for 13 weeks. The rabbit and dog displayed clinical signs of neurotoxicity such as convulsions, head bobbing, rapid blinking, tremors, tetany, lateral recumbency, salivation and incoordination in the 13-week inhalation toxicity studies. These signs occurred at the study LOAEL in the dog and at an exposure level exceeding the study LOAEL in the rabbit.

Neurotoxicity studies conducted in rats demonstrated that repeated exposures for 13 weeks to sulfuryl fluoride results in slowed somatosensory and visual evoked potentials as well as auditory brainstem and cortical responses. None of these electrodiagnostic parameters were affected following two exposures to sulfuryl fluoride. The brain lesions observed in the repeated-inhalation toxicity studies were also noted in the 13-week neurotoxicity study at exposure levels above those that affected evoked potentials, which appear to be a more sensitive indicator of neurotoxicity than neuropathology following sulfuryl fluoride exposure. No neuropathology was observed in the acute or one-year neurotoxicity studies. The brain lesions noted in the sulfuryl fluoride toxicology database indicate that sulfuryl fluoride targets a specific region of the brain as opposed to a particular neural cell type. Brain lesions were generally seen in the basal ganglia region of the brain, primarily affecting the caudate-putamen region.

Following chronic exposure of mice, rats and dogs to sulfuryl fluoride, similar effects were noted on the respiratory system, brain, kidneys and teeth as those observed following subchronic inhalation exposures. In the dog, dental fluorosis and lung effects (alveolar inflammation, aggregates of alveolar macrophages) were noted at the study no observed adverse effect level (NOAEL) following one year of exposure, while malacia of the caudate-nucleus region of the brain, renal toxicity (elevated blood urea nitrogen, dilation of the renal tubules with proteinaceous casts) and deaths/moribundity were noted at the next higher exposure level. In mice exposed for 18 months, increased mortality, brain vacuolation and respiratory tract effects (hyperplasia of epithelial cells of the larynx, congestion of the lungs, hyperplasia in the trachea) were noted at the highest level tested. Rats exposed for two years exhibited dental fluorosis and foci in the lungs at the study LOAEL, with significant renal toxicity and mortality (due to advanced chronic renal disease) as well as brain vacuolation occurring at the next highest exposure level. The renal toxicity of sulfuryl fluoride may be related to the fluoride ion, the primary metabolite of sulfuryl fluoride, because mammalian toxicity studies demonstrate that the fluoride ion tends to accumulate in renal tubules and cause renal nephrosis.

There was no evidence of oncogenic potential in long-term studies conducted in rats or mice. In particular, there was no increase in the incidence of bone tumours following exposure to sulfuryl fluoride. Sulfuryl fluoride did not cause point mutations in bacterial systems and was not associated with unscheduled DNA synthesis in vitro. Sulfuryl fluoride was negative for the induction of micronuclei in vivo in bone marrow cells. Sulfuryl fluoride was positive in an in vivo mammalian cell gene mutation assay, but the results indicated an effect on chromosomes as opposed to DNA. Sulfuryl fluoride also tested positive for chromosomal aberrations in vitro. It is possible that these effects stem from exposure to the fluoride ion, which has been shown to induce clastogenicity. Overall, the weight of evidence suggests that sulfuryl fluoride is not genotoxic.

Rat and rabbit developmental toxicity studies and a two-generation rat reproduction study indicated that sulfuryl fluoride was neither a developmental nor a reproductive toxicant. In the developmental toxicity studies, there were no adverse effects on rat fetuses at doses that were maternally toxic to the dams (reduced body-weight gains), and the effects on rabbit fetuses (reduced fetal weights, pale liver) occurred at doses that were also toxic to the dams (reduced body weight loss). In the reproductive toxicity study, effects in offspring at the study LOAEL were limited to stomach void of milk upon clinical examination while parental animals at this dose level displayed body-weight reductions, lung foci and aggregates of alveolar macrophages. The F_1 generation did not demonstrate any additional reproductive toxicity as a result of in utero exposure. Further, the incidence and severity of brain vacuolation, a critical endpoint of toxicity in the sulfuryl fluoride database, was similar in P and F_1 animals sacrificed as adults at the end of their respective reproductive phases.

Taken together, the developmental toxicity and reproductive toxicity studies did not provide evidence of increased sensitivity of the young on the basis of a comparison of NOAELs for endpoints examined. However, fetal and pup brains were not examined histologically in the developmental toxicity and reproductive toxicity studies; therefore, it is not known whether adverse effects on the brain would occur as a result of in utero exposure or exposure through

milk. In addition, it is not clear how effects on the brain might translate to adverse functional outcome (e.g., cognitive ability). For this reason, there remains uncertainty regarding the potential for developmental neurotoxicity in humans. In the absence of a developmental neurotoxicity study or other such study/data to address this concern, an additional uncertainty factor of three will be used for risk assessment purposes.

In special, non-guideline studies, high levels of sulfuryl fluoride induced incapacitation of rats within 6 to 42 minutes of exposure. Pretreatment with anticonvulsants (diazepam and diphenylhydantoin) appeared to protect against convulsions during exposure to sulfuryl fluoride, but did not prevent convulsions from occurring after exposure unless additional doses of anticonvulsant were administered. Treatment with calcium gluconate, a therapeutic treatment for fluoride toxicity, did not protect against the effects of sulfuryl fluoride. Exposure to sulfuryl fluoride caused laboured and irregular breathing, decreased respiratory and heart rates, increased blood pressure, and decreased lung tidal and minute volumes. The heart rate then increased significantly in rats prior to death. These findings indicate that sulfuryl fluoride is a pulmonary irritant as opposed to a sensory irritant, which would cause symptoms such as decreased respiratory frequency as well as eye and upper respiratory tract irritation. It was postulated that death may be associated in some manner with the blocking of the endogenous energy-producing process of oxidative phosphorylation in glycolysis. An ultrastructural assessment of the lungs of rats following inhalation exposure to high levels of sulfuryl fluoride revealed cellular swelling and focal protrusions. Some rats became moribund in the absence of significant pulmonary injury, indicating that changes to the cellular structure of the lungs are probably not a direct cause of death following exposure to sulfuryl fluoride.

Epidemiological studies on fumigators working with sulfuryl fluoride have shown that these workers exhibit impaired extremity motor and sensory activity, vision problems and impaired cognitive function. Several human fatalities have been reported following exposure to sulfuryl fluoride, most of which resulted from re-entering a fumigated building before it was cleared for re-entry.

3.2 Determination of Acceptable Daily Intake

The database contained no acceptable repeated-dose oral toxicity studies for deriving the acceptable daily intake (ADI). Instead, the two-year combined inhalation toxicity/oncogenicity study in the rat with a NOAEL of 5 ppm (5 mg/kg bw/day) was selected. This study was chosen as it was of appropriate duration and provided the lowest NOAEL of the database. In addition to effects on the respiratory system (lung foci), decreased body-weight gain, hematological and clinical chemistry findings as well as dental fluorosis were also observed at the study LOAEL of 20 ppm (20 mg/kg bw/day). The same NOAEL was established for parental systemic toxicity in the two-generation reproduction study in the rat because similar effects were noted (decreased body weight in females, foci in the lungs of males and aggregates of alveolar macrophages in both sexes).

In establishing the ADI, the PMRA considered the results from the metabolism study suggesting that at least 12% to 18% of the inhaled sulfuryl fluoride is absorbed. The PMRA did not consider it appropriate to apply an inhalation absorption factor to the NOAEL for dietary risk assessment because of the uncertainty regarding the validity of the values obtained from the metabolism study. In this study, no indication of the recovery efficiency of the analytical methods used was provided; therefore, the actual inhalation absorption may have been underestimated in this study. Furthermore, the inhalation absorption value was obtained from one test species following a single four-hour inhalation exposure. Extrapolation of this value to humans may not be valid. The United States Environmental Protection Agency (USEPA) did not apply an absorption factor to the NOAEL in deriving their chronic reference dose (USEPA 2004b). The European Union predicted an absorption value of 10% to 14% from the same study and used a worst-case absorption factor of 10% for their derivation of the ADI (European Union 2002). The California Department of Pesticide Regulation determined an absorption rate of 16% to 18%, again from the same study, but used the higher rate of 18% as this corresponded to the absorption following exposure to 30 ppm (Cal-DPR 2005a).

For calculation of the ADI, an uncertainty factor (UF) of 300 was deemed appropriate. This UF is based on the standard UF of 100 (10 for extrapolating from animals to humans; 10 to account for variability within a species) as well as an extra factor of 3 to account for uncertainty regarding the potential for neurotoxicity in the young as a result of a lack of a developmental neurotoxicity study. The resultant ADI is as follows:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{UF}} = \frac{5 \text{ mg/kg bw/day}}{300} = 0.017 \text{ mg/kg bw/day}$$

Selection of the NOAEL of 5 mg/kg bw/day from the 2-year rat study provides adequate protection for pathological changes in the brain (vacuolation, malacia) observed in several test species. The 13-week rabbit study provided the lowest NOAEL (18 mg/kg bw/day) in the repeat-dose studies for brain pathology with the LOAEL set at 59 mg/kg bw/day. In addition to the 300 UF noted above, an additional UF of 3 for extrapolation from subchronic to chronic would be applied to the NOAEL of 18 mg/kg bw/day, resulting in a nearly identical ADI. This ADI also provides an adequate margin of safety (MOS > 4000) to renal toxicity noted at 80 ppm (80 mg/kg bw/day) in the 2-year rat study, which provided the lowest NOAEL in the database for effects on the kidney.

A tolerable daily intake of 0.122 mg/kg bw/day was recommended for the assessment of the risks from ingestion of fluoride residues in treated commodities. Health Canada established this tolerable daily intake in the *Guidelines for Canadian Drinking Water Quality* (Health Canada 1996), based on the daily fluoride intake that is unlikely to produce moderate to severe dental fluorosis in children aged 22 to 26 months old. No UF was applied to the derivation of the tolerable daily intake because the daily intake level was based on studies of the most susceptible age group in the human population (Health Canada 1996).

Comparison of the proposed ADI for sulfuryl fluoride and the established tolerable daily intake for fluoride indicates that the overall contribution to fluoride intake would be minimal.

3.3 Acute Reference Dose

The acute neurotoxicity study in the rat with a study NOAEL of 291 ppm (291 mg/kg bw) was selected for the derivation of the acute reference dose (ARfD). No adverse effects were noted in this study in which rats were exposed to sulfuryl fluoride for six hours/day over two days. This study evaluated the critical endpoint of neurotoxicity. No neuropathology was evaluated in this study, but an assessment of evoked potentials was conducted, which was a more sensitive indicator of neurotoxicity than neuropathology following sulfuryl fluoride exposure in the 13-week neurotoxicity study.

For the reasons noted above for the ADI determination, the PMRA did not consider it appropriate to apply an inhalation absorption factor. The USEPA did not set an ARfD as they felt that no hazard was attributable to a single exposure to sulfuryl fluoride. Consistent with their approach for the ADI, the Eureopen Union applied a 10% inhalation absorption factor in deriving their ARfD.

For calculation of the ARfD, the standard UF of 100 (a factor of 10 for interspecies extrapolation and a factor of for intraspecies variability) was deemed appropriate. The resultant ARfD is as follows:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{UF}} = \frac{291 \text{ mg/kg bw}}{100} = 2.91 \text{ mg/kg bw}$$

The only oral studies of a duration relevant to the establishment of an ARfD consisted of older acute toxicity studies, which were considered unacceptable due to the limited information provided in the study report.

While of appropriate duration in the consideration of setting an ARfD, effects on maternal body weights noted at 225 mg/kg bw/day in the rat developmental toxicity study were difficult to attribute to a single dose.

In rats following two 6-hour exposures in the 2-week range-finding study, deaths occurred at higher exposure concentrations than those used in the acute neurotoxicity study, in which no adverse effects were noted. In other 2-week inhalation toxicity studies, effects did not occur until after the fifth exposure in rabbits (convulsions) and dogs (tremors and tetany), and until after the eighth exposure in mice (deaths). No toxic effects occurred earlier during the first week of exposures in the studies of longer duration, in which the highest concentration tested was generally lower than the exposure levels that caused effects within 2 to 8 days.

3.4 Toxicological Endpoint Selection

3.4.1 Occupational and Bystander Risk Assessment

The risk assessment for ProFume Gas Fumigant considered exposure of workers conducting fumigation and aeration activities, of mill workers entering mills following fumigation and aeration, and of bystanders residing in the vicinity of treated mills. Exposure of fumigation workers is expected to occur, intermittently, over a period of approximately five months (from May to October), with fumigations normally scheduled over long weekends. Mill workers entering fumigated mills may be exposed to residual sulfuryl fluoride in indoor air. As sulfuryl fluoride has been shown to dissipate rapidly, exposure of mill workers to sulfuryl fluoride is expected to be of acute duration and is not expected to last more than one or two days. Exposure of bystanders is considered to be of acute duration (24 hours), with exposure occurring only once or twice per year. The primary route of exposure is via the inhalation route.

In subchronic and chronic inhalation toxicity studies, toxicologically significant effects included lesions of the brain and respiratory tract as well as renal toxicity. Sulfuryl fluoride is not acutely neurotoxic, carcinogenic or mutagenic; it is extensively and rapidly metabolised and almost completely excreted within 24 hours. There is evidence of increased toxicity with increased duration of exposure as NOAELs for the 2- and 13-week studies were generally higher than those for the chronic studies. Sulfuryl fluoride is not a reproductive or developmental toxicant. No evidence of increased sensitivity of the young was demonstrated in the developmental toxicity and reproductive toxicity studies. However, fetal and pup brains were not examined histologically in these studies; therefore, it is not known whether adverse effects on the brain would occur as a result of in utero exposure or exposure through milk. In addition, it is not clear how effects on the brain might translate to adverse functional outcome (e.g., cognitive ability). In view of the uncertainty regarding the potential for neurotoxicity in the young, an additional factor of three was deemed appropriate for risk assessments that are not of an acute duration.

3.4.2 Acute Inhalation

The NOAEL of 291 ppm (291 mg/kg bw/day) from the acute neurotoxicity study in the rat was considered to be the most appropriate effect level to use for an acute inhalation risk assessment for workers entering fumigated mills and for bystanders. No adverse effects were noted in this study, in which rats were exposed to sulfuryl fluoride for six hours/day over two days. This study evaluated the critical endpoint of neurotoxicity. Neuropathology was not evaluated in this study, but an assessment of evoked potentials was conducted, which was a more sensitive indicator of neurotoxicity than neuropathology following sulfuryl fluoride exposure in the 13-week neurotoxicity study.

A target margin of exposure (MOE) of 100 (a factor of 10 for interspecies extrapolation and a factor of 10 for intraspecies variation) was deemed appropriate. Dividing the NOAEL of 291 mg/kg bw (291 ppm) by the target MOE of 100 results in a reference concentration of 2.91 mg/kg bw (2.91 ppm).

Deaths were noted in some rats exposed to sulfuryl fluoride for 6 hours over 1 or 2 days at a concentration of approximately 600 ppm. This concentration is roughly 200 times higher than that selected for the acute inhalation risk assessment (i.e., the reference concentration of 2.91 ppm) and 600 times higher than the re-entry level of 1 ppm, which is stipulated on the proposed label as the cut-off concentration above which workers are required to wear respiratory protection. In other species, effects did not occur until after the fifth exposure in rabbits (convulsions) and dogs (tremors and tetany), and until after the eighth exposure in mice (deaths) at exposure levels ranging from 30 ppm to 100 ppm. No toxic effects occurred earlier during the first week of exposures in studies of longer duration.

3.4.3 Intermediate-term Inhalation

The NOAEL of 30 ppm (18 mg/kg bw/day) from the 13-week inhalation toxicity study in the rabbit was considered appropriate to use for the intermediate-term inhalation risk assessment. This NOAEL was based on reduced body-weight gain, elevated serum fluoride levels, decreased liver weight and cerebral vacuolation (one female) at the LOAEL of 100 ppm (59 mg/kg bw/day). More severe brain pathology occurred at the next highest dose level (199 mg/kg bw/day).

This study is considered the most appropriate for this exposure scenario and provides the lowest NOAEL to an endpoint of concern (brain lesions) when compared to the other 13-week inhalation toxicity studies conducted in other species.

A target MOE of 300 was deemed appropriate. In addition to the standard UF of 100 (a factor of 10 for interspecies extrapolation and a factor of 10 for intraspecies variability), an extra factor of 3 was applied to the target MOE to account for the uncertainty regarding the potential neurotoxic effects in the young in the absence of a developmental neurotoxicity study.

3.5 Impact on Human and Animal Health Arising from Exposure to the Active Substance or to its Impurities

3.5.1 Operator Exposure Assessment

3.5.1.1 Handler Exposure and Risk

Fumigation workers could be exposed to sulfuryl fluoride while performing fumigation and aeration activities. No mixing or loading is required because ProFume Gas Fumigant is introduced directly to the area requiring treatment from the cylinder through a suitable leak-proof tube. Exposure of fumigation workers is expected to occur, intermittently, over a period of approximately five months (from May to October), with fumigations normally scheduled over long weekends. Each of approximately 50 mills is likely to be treated once per year, with a few mills being treated up to twice per year. Based on these considerations, the expected duration of exposure for fumigation workers is intermittent over an intermediate-term duration.

The primary route of exposure is inhalation. Dermal exposure is not expected to be of concern due to the high vapour pressure of sulfuryl fluoride (1.6×10^6 Pa at 20°C) and the proposed delivery system of ProFume Gas.

The fumigation and aeration of each mill is performed by a minimum of two trained fumigators, with at least one being licenced provincially. Typical fumigation tasks include moving the cylinders, connecting and disconnecting the hoses from the cylinders, maintaining the hoses and activating the introduction of the fumigant to the mill. Typical aeration tasks include starting aeration fans, unsealing aeration ducts, removing external plastic sheeting as well as opening doors and windows from the outside of the structure. Fumigators and aerators may also need to enter the building during the fumigation or aeration procedures for various reasons. Fumigation and aeration tasks may be performed by the same individuals.

To estimate worker exposure, personal air monitoring data collected for fumigators and aerators at cereal mills in the United States fumigated with ProFume Gas Fumigant were used. Duplicate personal air concentration samples were collected separately for workers performing fumigation tasks and aeration tasks at three mills. Personal air concentration replicates were collected for ten fumigation workers and eight aeration workers at these sites. These data are summarized in Table 3.5.1.1.1.

Table 3.5.1.1.1 Summary of Personal Air Sampling Data for Fumigation Workers

	Arithmetic Mean ($\mu g/m^3$)	**Arithmetic Mean (ppm)**
Fumigators (n=10)	31 740 ± 24 924	7.61 ± 5.97
Aerators (n=8)	6983 ± 6142	1.67 ± 1.47
All Workers (n=18)	20 728 ± 22 472	4.97 ± 5.39

Worker exposure was calculated using the arithmetic mean concentration of sulfuryl fluoride (in $\mu g/m^3$) and the following assumptions: an inhalation rate of 1 m^3/hr (NAFTA 1999), an exposure duration of 4 hours for fumigation activities and 4 hours for aeration activities, workers are assumed to work a total of 8 hours in a 24 hour period), and a body weight of 70 kg (NAFTA 1999).

Respiratory protection is required to achieve the target MOEs, as in the absence of respiratory protection MOEs range from 8 to 45. MOEs for workers wearing self-contained breathing apparatus (SCBA) are provided in Table 3.5.1.1.2.

Table 3.5.1.1.2 Exposure and Risk Estimates for Fumigation Workers Using ProFume Gas Fumigant With a 99.9% Protection Factor for Self-Contained Breathing Apparatus (SCBA)

Workers	Exposure (µg/kg bw/day)	MOE*
Fumigators	1.8	9900
Aerators	0.4	45000
Fumigator + Aerator	2.2	8100

* MOEs are calculated based on an intermediate-term NOAEL of 18 mg/kg bw/day from a 13-week rabbit study. The target MOE is 300.

An acceptable worker exposure level, that is the concentration to which a worker may be exposed over an 8-hour workday and have an MOE above the target MOE of 300, was calculated to be 0.13 ppm, based on an intermediate-term NOAEL of 18 mg/kg bw/day.

The following uncertainties were noted in the exposure and risk assessment.

- The estimated risk for fumigation workers using ProFume Gas Fumigant was based on data collected during five fumigations at three separate mills in the United States. The average Canadian mill volume is 2.8- to almost 20-fold higher than the volume of the mills fumigated in the American air monitoring studies and mill size may affect fumigation worker exposure.

- The exposure duration for fumigation workers was assumed to be eight hours per day, four hours performing fumigation activities and four hours performing aeration activities based on exposure durations for workers in the submitted air monitoring studies. This assumption may be conservative as there is usually a period between the introduction of the fumigant and the aeration of the building during which the fumigation workers may leave the site. Alternately, it may take longer to fumigate larger facilities, in which case these exposure durations may underestimate worker exposure.

- During the review of the air monitoring studies, some issues were noted with the analytical methods used in the studies, which indicate the monitoring data presented in the studies may underestimate the actual sulfuryl fluoride concentrations in the air of exposed fumigation workers.

As such, air monitoring data representative of Canadian climatic conditions will be generated by the registrant as a postregistration data requirement.

3.5.1.2 Postapplication Exposure and Risk

Mill workers entering treated mills to perform regular work tasks after fumigation and aeration have the potential to be exposed to residual sulfuryl fluoride. The exposure duration for these workers is expected to be acute (24 hours or less) because the vapours dissipate quickly.

The proposed label states that fumigated structures must be aerated to a concentration of 1 ppm prior to entering the building. This is consistent with the re-entry level of 1 ppm for ProFume in the USEPA's Corrected Human Health Assessment for Sulfuryl Fluoride (USEPA 2004a). The MOE for mill workers entering treated mills aerated to this concentration was calculated to be 610 based on an 8-hour exposure duration and an inhalation rate of 1 m^3/hr. This figure is above the target MOE of 100 (using an acute NOAEL of 291 mg/kg bw/day) and may be a conservative estimate as it is based on a worker being exposed to a sulfuryl fluoride concentration in air of 1 ppm for the entire 8-hour work period.

3.5.2 Bystander Exposure Assessment

There is potential for acute inhalation exposure of bystanders during fumigation and aeration as well as after aeration while sulfuryl fluoride vapours disperse from the treated site. Exposure of bystanders (adults and children living in residences near a mill that may be treated once or twice per year) could occur up to twice per year. The exposure duration is expected to be acute (up to 24 hours).

To estimate bystander exposure, ambient air sampling data collected at four separate fumigation events in the United States were combined. Of the four fumigations that were used to estimate bystander exposure, three were conducted at a site in Indiana and one at a site in Kansas.

An average 24-hour air concentration for each monitoring location was estimated by considering the three 8-hour ambient air concentrations at each site during fumigation. When the fumigation period was less than 24 hours, the average 24-hour concentration was based on the available 8-hour samples. The calculated mean and 95th percentile values of the mean 24-hour ambient air sulfuryl fluoride concentrations for various distances from the treated mill are presented in Table 3.5.2.1.

Table 3.5.2.1 Summary of the 24-Hour Average Ambient Air Concentrations for Various Distances from the Treated Mills (based on 8-hour sampling during the fumigation period)

Distance from Mill (m)	Sample Size	Arithmetic Mean µg/m^3 (ppm)	Standard Deviation µg/m^3 (ppm)	95th Percentile µg/m^3 (ppm)
5	32	9472 (2.27)	16 346 (3.92)	28 883 (6.92)
10	17	8943 (2.14)	12 405 (2.97)	23 753 (5.69)
25	29	3085 (0.74)	5524 (1.32)	11 451 (2.75)
50	22	1375 (0.33)	1768 (0.42)	5859 (1.40)
75	20	1158 (0.28)	1483 (0.36)	4090 (0.98)
>100	4	1676 (0.40)	1405 (0.34)	3203 (0.77)

The total volume of the mills in the studies are 4.5- to almost 20-fold smaller than for the average mill in Canada. Due to uncertainty associated with applying this data to the range of use sites in Canada, the limited number of sites, as well as uncertainties associated with the analytical methods used in the studies, it was considered appropriate to use the 95th percentile of the 24-hour average sulfuryl fluoride concentrations at each distance to calculate bystander exposures. Ambient air concentrations measured during fumigation were used as the sulfuryl fluoride concentrations were generally higher during the fumigation phase compared to the aeration phase.

Bystander exposure was calculated assuming an inhalation rate of 13.3 m^3/day for adults and 8.3 m^3/day for children (NAFTA 1999), an exposure duration of 24 hours, and a body weight of 70 kg for adults and 15 kg for children (NAFTA 1999).

Table 3.5.2.2 24-Hour Exposure and Risk Estimates for Bystanders at Various Distances from Treated Mills

Distance from Mill (m)	Exposure to Adults (µg/kg bw/day)	MOE for Adults*	Exposure to Children (µg/kg bw/day)	MOE for Children*
5	5500	53	16000	18
10	4500	64	13000	22
25	2200	130	6300	46
50	1100	260	3200	90
75	780	370	2300	130
>100	610	480	1800	160

* MOEs are calculated based on an acute term NOAEL of 291 mg/kg bw/day from an acute neurotoxicity study in the rat. The target MOE is 100.

The 24-hour risk estimates exceed the target MOE (i.e., are acceptable) at a distance of 25 m from the treated mill for adults and approach the target MOE (i.e., are acceptable) at a distance of 50 m from the treated mill for children.

Similarly, risk estimates were calculated for adults and children exposed to sulfuryl fluoride for 8 hours, which is considered to be typical of exposure in commercial settings (i.e., offices, restaurants, stores). The 95th percentiles of all 8-hour time-weighted average air concentrations measured at various distances from the treated mills were used to calculate exposure. Risk levels were similar to those calculated for the 24-hour period above. Specifically, the 8-hour risk estimates exceed the target MOE at a distance of 10 m from the mill for adults and at 50 m for children.

Risk estimates for adults and children exposed to a sulfuryl fluoride concentration of 1 ppm for 24 hours were above the target MOE (370 and 130 for adults and children, respectively) based on an acute NOAEL of 291 mg/kg bw/day.

The following uncertainties were noted in the bystander exposure and risk assessment.

- The ambient air monitoring data used in the bystander risk assessment were collected during fumigations at two separate mills in the United States. It is not known how representative this data is of Canadian scenarios. For example, meteorological data play an important role in the distribution of fumigants. The absence of data for mill fumigation under Canadian climatic conditions is a significant limitation.

- In addition, the monitoring data presented in the studies may underestimate the actual sulfuryl fluoride concentrations in ambient air due to limitations of the analytical methods.

As such, air monitoring data representative of Canadian climatic conditions will be generated by the registrant as a postregistration data requirement.

Based on the above results, two bystander risk management options were identified:

- establish buffer zones in the vicinity of mills being fumigated—bystanders within the buffer zones would be vacated prior to initiation of fumigation; or

- establish site-specific fumigation management plans.

Establishment of site-specific fumigation management plans was determined to be more operationally feasible while at the same time ensuring bystander protection. The site-specific fumigation management plans will include the following critical elements:

- air monitoring sampling strategies to ensure comprehensive monitoring of sulfuryl fluoride in ambient air within a minimum 50 m radius of the structure being fumigated; and

- an evacuation plan to be implemented if concentrations of sulfuryl fluoride, as measured by approved detection devices of sufficient sensitivity (limit of detection [LOD] less than or equal to 1 ppm) such as the Interscan (Model GF 1900) or Miran gas analyzer (SapphIRE), exceed 1 ppm.

3.5.2.1 Uncertainties and Conservatisms in the Bystander Risk Assessment

The ambient air monitoring data used in the bystander risk assessment were collected during four fumigations at two separate mills in the United States. Data from the California site were excluded due to low field recovery; however, uncorrected data were high for this site (up to 9 ppm, 5 m from the mill during fumigation and up to 10 ppm, 10 m from the mill during aeration) and the fumigation period was long (34 hours). Therefore, its exclusion may underestimate combined ambient air concentrations.

It is not known how representative this American data is of Canadian scenarios. As meteorological data play an important role in the distribution of the fumigant, the absence of data for mill fumigation under Canadian climatic conditions is a significant limitation. Similarly, the construction of the mill is important in determining how well the fumigant is contained within the structure during the fumigation process. The mills in the study were made of corrugated metal sheeting, which is not expected to contain the fumigant well, as was demonstrated by the short half-loss time and high ambient air concentrations measured during the fumigation phase, particularly for the Indiana mill. Therefore, the ambient air concentrations are not expected to underestimate air concentrations in a typical mill of that size. The average Canadian mill volume

is expected to be higher than the volume of the mills that were fumigated in the American air monitoring studies. It is not known if larger mills would result in higher ambient air concentrations around the treated structure.

As was noted previously, the monitoring data presented in the studies may underestimate the actual sulfuryl fluoride concentrations in ambient air due to limitations of the analytical methods. To account for these uncertainties, the 95th percentile of the 24-hour mean ambient air concentration was used to estimate 24-hour bystander exposure, and the 95th percentile of the 8-hour time weighted average air concentrations was used to estimate 8-hour bystander exposure.

An average 24-hour air concentration for each monitoring location was estimated by considering the three 8-hour ambient air concentrations at each site during fumigation. In some cases the average 24-hour concentration was based on 1 or 2 available 8-hour samples. In these cases, the 24-hour estimate is expected to overestimate the 24-hour mean sulfuryl fluoride concentration because the samples that were lost were generally in the second and third 8-hour period and the concentration in the earlier periods, when sulfuryl fluoride concentrations were generally higher, was extrapolated to the whole 24-hour period. However, a 24-hour exposure duration may underestimate bystander exposure if the fumigation period is longer than 24 hours. The duration of the fumigation phase in the American studies varies from 16 to 35 hours; the mean duration is 26.5 hours.

Another uncertainty in the bystander risk assessment is that bystanders were assumed to be exposed to ambient air concentrations of sulfuryl fluoride measured around the mill during fumigation for 24 or 8 hours. This assumes that the individual remains in the residence for 24 hours or in a commercial building for 8 hours, and that the concentration of sulfuryl fluoride is the same in indoor air as in outdoor air measured at 1.5 m above the ground.

4.0 Residues

No food uses are proposed for the Canadian registration of sulfuryl fluoride at this time. As such, a food residue assessment is not required.

5.0 Fate and Behaviour in the Environment

The USEPA did not conduct an environmental risk assessment on sulfuryl fluoride in 1992, stating that "...sulfuryl fluoride is registered for highly specialized uses, and due to its chemical properties, EPA is not requiring the usual supporting environmental fate data for reregistration. After fumigation and aeration of treated structures, there is little likelihood that non-target organisms would be exposed to residues of sulfuryl fluoride, or that the pesticide would leach to ground water. Residues of the parent chemical are not expected to remain in the environment for any significant length of time." The USEPA also indicated that toxicity to organisms was not assessed because, "based on its limited use sites and chemical properties, significant environmental exposure is not expected to result from use of sulfuryl fluoride" (USEPA 1992).

5.1 Physical and Chemical Properties Relevant to the Environment

Sulfuryl fluoride is a gas under environmentally relevant conditions (boiling point of -55°C). The vapour pressure is reported to be 1.6×10^6 Pa, which is very high volatility under field conditions according to Kennedy and Talbert (1977). The Henry's law constant ranges from 1.56 to 2.16 atm m^3/mole (variation in value is due to range in solubilities reported) and, according to Mackay and Wolkoff (1973), has a potential to volatilize. The Henry's law constant is 1.1 to 1.5, which indicates rapid loss from a water surface or moist soil according to the USEPA (1975a). In the literature, there are slightly different values reported for Henry's law constant. The California Department of Pesticide Regulation reports the Henry's law constant to be 0.0328 atm m^3/mole (Cal-DPR 2005b). Based on the other data presented in the document, the PMRA calculated a value of 2.1 atm m^3/mole. The solubility in water is reported to be either 750 mg/L (Tomlin 2004, Cal-DPR 2005b) or 1040 mg/L (applicant). Both values indicate that sulfuryl fluoride is very soluble in water. A K_{ow} of 2.57 was reported in a document published by the Cal-DPR. This results in a log K_{ow} of 0.41; therefore, bioconcentration is unlikely according to the USEPA (1975b). This data was also found in the Material Safety Data Sheet (MSDS) for sulfuryl fluoride. In the fugacity model study submitted, a log K_{ow} of 0.14 was used. This information was cited to a study by Ghaoui and Comb (2001) conducted for the applicant; however, this study was not submitted. Therefore, the value of 0.41 from the MSDS sheet and the Cal-DPR report will be used (Appendix II, Table 1).

Based on the chemical and physical data available for sulfuryl fluoride, it is not expected to partition to soil or water. Therefore, this risk assessment focusses on the fate in the atmosphere as well as the toxicity and potential risk to organisms via inhalation.

Monitoring studies conducted during the fumigation and aeration of mills were provided. These data were used in the risk assessment as well as in the ISCST3 model (USEPA 1995a) to model air concentrations under Canadian use scenarios.

5.2 Summary of Fate and Behaviour in the Environment

Sulfuryl fluoride is expected to remain in the atmosphere after release from fumigated structures based on the fugacity model, the vapour pressure (1.6×10^6 Pa), Henry's law constant (1.5–2.1) and the use pattern (release to the atmosphere). Once released to the atmosphere, sulfuryl fluoride is expected to persist for long periods of time (on the order of two decades) and is expected to be transported throughout the atmosphere (R.F. Weiss and J. Mühle 2005). There is no information regarding the transformation of sulfuryl fluoride in the lower or upper atmosphere. Modelling conducted by the applicant indicates that sulfuryl fluoride has a high 100-year Global Warming Potential (GWP) (278–477). The GWP is a method used to compare different compounds in the atmosphere in the determination of greenhouse gases. The GWP is defined as the ratio of the time-integrated radiative forcing from the instantaneous release of 1 kg of a trace substance relative to that of 1 kg of a reference gas (IPCC 2001). The 100-year GWP of 477 means that 1 kg of sulfuryl fluoride has the same effect as 477 kg of CO_2. The Cal-DPR has suggested that sulfuryl fluoride might be a greenhouse gas. Based on the GWP of 278–477, sulfuryl fluoride will be brought to the attention of the Greenhouse Gas Division of Environment Canada. The

PMRA currently has no policy with respect to the registration of greenhouse gases. No data are available on the transformation of sulfuryl fluoride in the upper or lower atmospheres.

Air concentration monitoring data adjacent to mills fumigated in the United States found air concentrations up to a maximum of 20 ppm (8.5×10^5 µg/m^3) within 5 m. Preliminary ISCST3 modelling of a generic mill fumigation under Canadian conditions resulted in estimated concentrations of 77 ppm (3.19×10^5 µg/m^3). Highest modelled concentrations occurred during winter periods.

6.0 Effects on Non-target Species

6.1 Toxicity

Sulfury fluoride has a complex mode of action. The primary toxicity is assumed to be through the action of the fluoride ion. It inhibits oxygen uptake, disturbs the normal phosphate balance and inhibits hydrolysis of fatty acids (Journal of Pesticide Reform 1997).

The inhalation toxicity of sulfuryl fluoride to rats and mice was assessed. Three acute inhalation studies were submitted and found acceptable (Appendix I, Table 1). Sulfuryl fluoride was found to cause mortality in 50% of the test rats at air concentrations of 4.14×10^6 and 4.69×10^6 µg/m^3 (991 and 1122 ppm) in females and males, respectively. In mice, the rates were 1.69×10^6 µg/m^3 (404 ppm) in one study and 2.68×10^6 (642 ppm) and 2.76×10^6 (660 ppm) µg/m^3 (females and males, respectively) in a second study. Two chronic mammalian inhalation studies were also reviewed; however, chronic exposure is not expected to occur, owing to the nature of sulfuryl fluoride and the use-pattern. No NOEC values were calculated in these studies; therefore, the acute inhalation endpoint will be calculated based on 1/10th of the LC_{50}. The rat and mouse acute inhalation endpoints are 4.14×10^5 (99.1 ppm) and 1.69×10^5 µg/m^3 (40.4 ppm), respectively, based on the lowest LC_{50} values.

The inhalation toxicity of sulfuryl fluoride to birds was not determined. Therefore, inhalation rates were estimated for birds based on the results from the rat and mouse studies. This was done by converting the mouse/rat LC_{50} to a LD_{50} and then dividing this by two factors: the ratio of the avian to mammalian pulmonary membrane diffusion rates of three (USEPA 2004b) and an extrapolation factor from laboratory to field for birds of three (USEPA 1993). This value was then converted back to a LC_{50} and then converted to an acute inhalation endpoint by dividing by a factor of 10.

Using the mouse inhalation LC_{50} of 1.69×10^6 µg/m^3 (404 ppm), the avian inhalation toxicity NOEL is 0.2×10^5 µg/m^3 (4.8 ppm) (based on a body weight of 100 grams).

The toxicity to earthworms and aquatic species was not assessed because sulfuryl fluoride is not expected to partition to water or soil. Therefore, these organisms are not expected to be exposed to sulfuryl fluoride.

6.2 Risk Assessment

The risk assessment integrates the exposure and ecotoxicology data to estimate the potential for adverse ecological effects. The PMRA currently conducts a deterministic risk assessment of pest control products. Environmental risk is characterized using the risk quotient method, which is the expected environmental concentration (EEC) divided by the toxicity endpoint. Risks are then classified, based on the scheme presented in Appendix II, Table 2. A screening level risk assessment was conducted based on the target application concentration of 128 g/m^3 (128 mg/L) to fumigate a structure (screening risk assessment).

6.3 Non-Target Arthropods

There are concerns regarding the toxicity to bees and other non-target beneficial insects within the vicinity of fumigation areas. Most mills in Canada are located in urban/industrial areas which, along with the infrequent use (expected maximum is twice a year), will may help to limit the exposure to these organisms.

6.4 Mammalian and Avian Inhalation Toxicity

The acute inhalation endpoint for the rat is 0.414×10^5 $\mu g/m^3$ and for the mouse is 0.169×10^5 $\mu g/m^3$. The risk quotient for sulfuryl fluoride is 309 for the rat and 757 for the mouse, which results in a very high risk to small mammals in the building during fumigation. The acute inhalation endpoint for a 100-gram bird was calculated to be 0.2×10^5 $\mu g/m^3$. The risk quotient for sulfuryl fluoride to birds is 6400, which results in an extremely high risk to birds.

In a refined risk assessment, monitoring data of air concentrations measured during fumigation were used. The maximum sulfuryl fluoride concentration measured 5 m from the building during a fumigation experiment was 85 451.1 $\mu g/m^3$ (20.5 ppm). The risk quotient for sulfuryl fluoride is 0.2 for the rat and 0.5 for the mouse. This results in a negligible to low risk to small mammals outside of the building during fumigation. The risk quotient for birds is 4.25, which results in a moderate risk to birds outside the building during fumigation. The modelling results return similar risk quotients.

The risk is associated with birds and mammals being on or near the building being fumigated. Given that programs are currently in place to discourage mammal and bird pests, mammals and birds are not expected to be present. Appendix II, Table 3 summarizes mammalian and avian risk.

6.5 Risk Summary

Sulfuryl fluoride presents a low risk to small mammals and a moderate risk to birds during the fumigation process. During aeration, it presents a negligible risk to small mammals and a low risk to birds. All organisms in a mill will be killed during fumigation. Given that programs are currently in place to discourage mammal and bird pests, mammals and birds are not expected to be present.

6.6 Overall Summary

With regards to fate, the primary issues appear to be longevity and mechanisms of transformation in the atmosphere. Fumigant concentrations are being modelled for fumigation and aeration around a site, and preliminary values have been presented; however, further work needs to be done.

Sulfuryl fluoride has a GWP of 278–477. This may indicate that sulfuryl fluoride is a greenhouse gas. This information will be forwarded to the Greenhouse Gas Division of Environment Canada upon publication.

With regards to toxicology, the primary exposure route of concern is inhalation. The greatest risk is to organisms within the immediate vicinity of the mill (birds, mammals and insects), via inhalation. Mill operators actively deter birds and mammals from residing on or near mills. Therefore, risk to these organisms is expected to be very minimal. With respect to insects (bees and beneficials), most of the mills (roughly 75%) are located in urban areas, which may help to limit exposure.

Sulfuryl fluoride presents a low risk to small mammals and a moderate risk to birds during the fumigation process. During aeration, it presents a negligible risk to small mammals and a low risk to birds. All organisms within a mill will be killed during fumigation. Given that the programs are currently in place to control mammal and bird pests in mills, mammals and birds are not expected to be present.

7.0 Efficacy

7.1 Effectiveness Against Target Organisms or with Respect to the Effect Achieved

7.1.1 Intended Use

Dow AgroSciences Canada Inc. has submitted an application to register ProFume Gas Fumigant (99.8% sulfuryl fluoride) for use in empty cereal grain mills, associated empty storage facilities and empty food processing facilities to control stored product pests such as Indian meal moth, confused flour beetle, saw-toothed grain beetle, warehouse beetle and granary weevil. The product proposed for registration must be applied by licensed applicators using the ProFume Fumiguide computer program, which identifies the parameters under which the fumigation can take place (e.g., maximum dose and concentration, minimum length of fumigation and temperatures).

7.1.2 Mode of Action

Sulfuryl fluoride is a fumigant that penetrates the insect's body through inhalation in actively respiring life stages or by diffusion into the egg, where it is broken down to the insecticidally active ingredient fluoride anion. Sulfuryl fluoride is considered a non-specific target poison acting by disrupting glycolysis and the citric acid cycle, thereby depriving the insect of the necessary energy for survival (Meikle et al. 1963). When glycolysis and the fatty acid cycle are inhibited, insects use protein and amino acids to maintain a viable energy level, but these alternative energy producing processes are insufficient to maintain the minimum metabolic rate required for survival.

7.1.3 Crops

This product has not been proposed for use on crops.

7.1.4 Effectiveness Against Pest

7.1.4.1 Confused Flour Beetle (*Tribolium confusum*)

In 37 laboratory bioassays conducted under a variety of conditions (from 4.4 to 26.6 °C for 1–72 hours), the LD_{95} to control adult confused flour beetle were all below the maximum target concentration of 128 g/m^3. Field studies conducted in Europe found 100% mortality in confused flour beetle eggs and adults at 28.0–31.4°C for 22.25 hours at doses between 1101 and 1501 g.h/m^3. This indicates that confused flour beetle control would be achieved under the parameters allowed in the ProFume Fumiguide (i.e., maximum dose of 1500 g.h/m^3). Field studies conducted in the United States demonstrated 100% control of confused flour beetle eggs, larvae, pupae and adults at 25.6–29.2°C for 13.5–62.2 hours at doses between 528 and 1407 g.h/m^3.

7.1.4.2 Red Flour Beetle (*Tribolium castaneum*)

In 35 laboratory bioassays conducted under a variety of conditions (from 20 to 30°C for 16–48 hours), the LD_{95} to control red flour beetle larvae, pupae and adults was below the maximum target concentration of 128 g/m^3 or a dose of 1500 g.h/m^3. Field studies conducted in Europe found 100% mortality of red flour beetle eggs and adults at 28.1–31.4°C for 22.25 hours at doses between 1101 and 1501 g.h/m^3. This indicates that red flour beetle control would be achieved under the parameters allowed in the ProFume Fumiguide (i.e., maximum dose of 1500 g.h/m^3). Field studies conducted in the United States found 100% mortality of red flour beetle eggs, larvae, pupae and adults at 25.6–29.2°C for 13.5–34.75 hours at doses between 528 and 1407 g.h/m^3. This indicates that control of red flour beetles would be achieved under the parameters allowed in the ProFume Fumiguide (i.e., maximum dose of 1500 g.h/m^3).

7.1.4.3 Saw-toothed Grain Beetle (*Oryzaephilus surinamensis*)

In 41 laboratory bioassays conducted under a variety of conditions (from 20 to 30°C for 16–72 hours), the LD_{95} to control all life stages of saw-toothed grain beetles was below the maximum target concentration of 128 g/m^3 or dose of 1500 g/m^3. Field studies conducted in Europe found 100% mortality all life stages of saw-toothed grain beetles under the parameters allowed in the ProFume Fumiguide (i.e., maximum dose of 1500 g h/m^3). Field studies conducted in the United States found 100% mortality of all saw-toothed grain beetles life stages at 22.1–29.2°C for 13.5–32.0 hours at doses between 528 and 1483 g.h/m^3. This indicates that control of saw-toothed grain beetles would be achieved under the parameters allowed in the ProFume Fumiguide (i.e., maximum dose of 1500 g.h/m^3).

7.1.4.4 Indian Meal Moth (*Plodia interpunctella*)

In 53 laboratory bioassays conducted under a variety of conditions (from 15.6 to 30.0°C for 24–72 hours), 100% mortality of all Indian meal moth life stages was achieved at a concentration below the maximum target concentration of 128 g/m^3 or dose of 1500 g/m^3. Field studies conducted in Europe found 100% mortality of Indian meal moth eggs and pupae at 28.1–31.4°C when exposed for 22.25 hours at doses between 1101 and 1501 g.h/m^3. Field studies conducted in the United States found 100% mortality of Indian meal moth eggs, larvae and pupae at 26.2–29.2°C when exposed for 13.5–62.2 hours at doses between 528 and 1407 g.h/m^3. This indicates that control of Indian meal moths would be achieved under the parameters allowed in the ProFume Fumiguide (i.e., maximum dose of 1500 g.h/m^3).

7.1.4.5 Mediterranean Flour Moth (*Ephestia kuehniella*)

In 37 laboratory bioassays conducted under a variety of conditions (from 15.0 to 30.0°C for 24–72 hours), the concentration or dose required to achieve 100% mortality of all Mediterranean flour moth life stages was below the maximum target concentration of 128 g/m^3 or dose of 1500 g.h/m^3. Field studies conducted in Europe found 100% mortality of Mediterranean flour moth eggs and pupae at 28.1–31.4°C when exposed for 22.25 hours at doses between 1101 and 1501 g.h/m^3. This indicates that control of Mediterranean flour moths would be achieved under the parameters allowed in the ProFume Fumiguide (i.e., maximum dose of 1500 g.h/m^3).

7.1.4.6 Warehouse Beetle (*Trogoderma variabile*)

In 23 laboratory bioassays conducted under a variety of conditions (from 20.0 to 30.0°C for 48 hours), the concentration or dose required to achieve at least 95% mortality of warehouse beetle eggs was below the maximum target concentration of 128 g/m^3 or dose of 1500 g.h/m^3. However, control of warehouse beetle eggs at 15.6°C was unacceptable. Field studies conducted in the United States found 100% mortality of warehouse beetle eggs, larvae and pupae at 25.6–29.2°C when exposed for 13.5–47.8 hours at doses between 528 and 1407 g.h/m^3. This indicates that control of warehouse beetles would be achieved under the parameters identified in the ProFume Fumiguide (i.e., maximum dose of 1500 g.h/m^3).

7.2 Phytotoxicity to Target Plants or Target Plant Products

No crops or commodities are proposed for registration.

7.3 Impact on Succeeding Crops, Adjacent Crops and on Treated Plants or Plant Products Used for Propagation

No crops or commodities are proposed for registration.

7.4 Economics

Stored product insects cause direct physical damage and contaminate food destined for animal and human consumption. The economic loss caused by stored product insects in manufacturing and storage can be profound. Federal government legislation and foreign government directives on food quality and hygiene have set high standards for industry.

7.5 Sustainability

7.5.1 Survey of Alternatives

Fumigation to control stored product insects can be conducted using aluminum phosphide, magnesium phosphide, phosphine or methyl bromide. As methyl bromide is being phased out under the Montreal Protocol on Substances that Deplete the Ozone Layer, it cannot be considered an alternative to sulfuryl fluoride. The remaining registered alternatives (i.e., aluminum phosphide, magnesium phosphide and phosphine) are corrosive to electronic equipment, which makes millers and food processing facility operators reluctant to use these products. Therefore, in the proposed use sites aluminum phosphide, magnesium phosphide and phosphine cannot be considered alternatives.

7.5.1.1 Non-chemical Control Practices

Non-chemical control practices are common and integral in any control program for stored product insects. Good sanitation and inspection practices are used for pest management in the food industry. Heat treatment has been, and continues to be, evaluated as an alternative to chemical fumigation. To date, heat treatments are considered financially unfeasible by many due to the high cost of retrofitting older buildings to withstand high temperatures for a prolonged period of time.

7.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

Integrated pest management practices in cereal grain mills and food processing facilities to control stored product insects include sanitation, inspection, and selective or spot treatments with insecticides to control small or localised infestations. Fumigant treatments are used to reach stored product insect infestations located within the fabric of the building (e.g., crack and crevices, under floor boards) or within equipment.

7.5.3 Contribution to Risk Reduction

When empty cereal grain mills in Canada require fumigation, methyl bromide has historically been the most commonly used fumigant. However, methyl bromide has been identified as an ozone depleting substance under the Montreal Protocol and is being phased out. Sulfuryl fluoride is not an ozone depleting substance.

7.5.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Sulfuryl fluoride has been used in the United States for over 40 years to control termites and wood boring beetles. During this time, these insects have not developed any known resistance to the fumigant. There is also no known evidence of cross-resistance to sulfuryl fluoride in phosphine-resistant insects. Modelling for resistance to sulfuryl fluoride in stored product insects has shown that given the frequency of use and the life cycles of these pests, the risk of the development of resistance is low. Taking these factors into consideration, the applicant has planned no specific resistance management strategies.

The applicant has indicated that label statements, literature and training programs will advise that although the risk of stored product insect pests developing resistance to sulfuryl fluoride is low, fumigation should be used in association with other pest management practices, such as integrated pest management programs.

7.6 Conclusions

Sufficient efficacy data have been submitted to support the proposed use claims of control of stored product pests such as Indian meal moth, confused flour beetle, saw-toothed grain beetle, warehouse beetle and granary weevil in empty cereal grain mills, empty food processing plants and empty storage facilities (see Table 7.6.1).

7.6.1 Summary

Table 7.6.1 Summary of Proposed and Accepted Label Claims

	Proposed Label Claim	Supported Use Claim
Use site:	Empty cereal grain mills, storage facilities and food processing facilities	Empty cereal grain mills, empty storage facilities and empty food processing facilities
Pests:	Stored product pests such as Indian meal moth, confused flour beetle, saw-toothed grain beetle, warehouse beetle and granary weevil	Stored products pests such as Indian meal moth, confused flour beetle, saw-toothed grain beetle, warehouse beetle and granary weevil
Temperature: (booklet and manual)	Do not apply when temperatures within the commodity to be fumigated is below 4.4°C	Use when temperatures in the empty mill, empty storage facility or empty food processing plant are between 15.6 and 30°C
Pressure:	Normal atmospheric pressure	Normal atmospheric pressure
Dosage:	The maximum target dosage is 1500 CT with a maximum target concentration of 128 g·h/m^3	The maximum target dosage is 1500 CT with a maximum target concentration of 128 g·h/m^3

8.0 Toxic Substances Management Policy

During the review of ProFume, the PMRA has taken into account the federal Toxic Substances Management Policy[1] and has followed its Regulatory Directive DIR99-03[2]. It has been determined that this product does not meet TSMP Track 1 criteria for the following reasons:

- Sulfuryl fluoride does meet the criteria for persistence. Its value for half-life in air, estimated at 20 years, is greater the TSMP Track 1 cut-off criteria ≥2 days for air .
- Sulfuryl fluoride is not expected to bioaccumulate. As the *n*-octanol–water partition coefficient (log K_{ow}) is 0.41, which is below the TSMP Track 1 cut-off criterion of ≥5.0.
- Sulfuryl fluoride does meet the criteria for toxicity (see Section 6.4).

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1 The federal Toxic Substances Management Policy is available through Environment Canada's website at www.ec.gc.ca/toxics

2 Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, is available through the Pest Management Information Service. Phone: 1 800 267-6315 within Canada or (613) 736-3799 outside Canada (long distance charges apply); Fax: (613) 736-3798; E-mail: pmra_infoserv@hc-sc.gc.ca; or through our website at www.pmra-arla.gc.ca

- There is insufficient data to determine if sulfuryl fluoride forms any major transformation products that meet the TSMP Track 1 criteria.

- Sulfuryl fluoride (technical grade) does not contain any by-products or microcontaminants that meet the TSMP Track 1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

The formulated product does not contain any formulants known to contain TSMP Track 1 substances.

9.0 Regulatory Decision

The PMRA has carried out an assessment of available information in accordance with the Pest Control Products Regulations and has found it sufficient to allow a determination of the safety, merit and value of sulfuryl fluoride and ProFume Gas Fumigant. The Agency has concluded that the use of sulfuryl fluoride and the associated end-use product ProFume Gas Fumigant in accordance with the enclosed annotated labels has merit and value consistent with the Pest Control Products Regulations and does not entail an unacceptable risk of harm. The Agency has determined that these products are eligible for temporary registration pursuant to the Pest Control Products Regulations, subject to the terms and conditions outlined in the registration letter and summarized below:

- Submission of ambient air monitoring data measured around cereal mills treated with ProFume Gas Fumigant representative of Canadian climatic conditions; the protocol for this study should be approved by PMRA prior to study initiation.

- Development, in consultation with the PMRA, of a product stewardship program containing end-user training.

- Development of a fumigation management plan. The plan must include the following measures:
  - site characterisation;
  - appropriate monitoring of air concentrations around the site;
  - notification of all personnel;
  - procedures for sealing the premises, treating with fumigant and postapplication operations; and
  - an emergency response plan, including evacuation procedures.

Further studies that determine the transformation of sulfuryl fluoride in the lower and upper atmospheres may be required. The need and nature of these studies will be determined in consultation with Environment Canada. Any information deemed necessary will be required before a conversion to full registration can be completed.

In the absence of a developmental neurotoxicity study, an extra UF of three will be applied to all relevant risk assessments conducted for sulfuryl fluoride. This may have an impact on the acceptability of future use expansions. To refine the risk assessment and/or to support future use expansions, the submission of a developmental neurotoxicity study, or some modification thereof, conducted with sulfuryl fluoride would be required. It is recommended that the applicant consult with PMRA on the protocol to be used for this study prior to study initiation.

List of Abbreviations

ADI	acceptable daily intake
ALK	alkaline phosphatase
ALT	alanine aminotransferase
ARfD	acute reference dose
bw	body weight
Cal-DPR	California Department of Pesticide Regulation
CAS	Chemical Abstracts Service
CK	creatine kinase
CT	concentration × time
ECG	electrocardiogram
EEG	electroencephalogram
F_1	first filial generation
F_2	second filial generation
FSO_2	fluorosulfate
g	gram(s)
GD	gestation day
GWP	global warming potential
Hg	mercury
IPCC	Intergovernmental Panel on Climate Change
kg	kilogram(s)
K_{ow}	*n*-octanol–water partition coefficient
L	litre(s)
LD	lactation day
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
mg	milligram(s)
mm	millimetre(s)
MOE	margin of exposure
NAFTA	North American Free Trade Agreement
nm	nanometre(s)
NOAEL	no observed adverse effect level
OSHA	Occupational Safety and Health Administration
P	parental generation
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
ppm	parts per million
SCBA	self-contained breathing apparatus
SO_2	sulfate
TSMP	Toxic Substances Management Policy
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
1/H	Henry's law constant
°C	degree(s) Celsius

Appendix I Toxicology

Table 1 Toxicology Summary Tables

Unless otherwise specified, air concentrations are presented as analytical concentrations, effects listed were noted in both males and females, changes in relative organ weights were those relative to body weight, and inhalation exposures to sulfuryl fluoride gas were conducted under dynamic airflow conditions. Food and water consumption were generally not measured.

METABOLISM
Rate and extent of absorption: Radiolabelled (^{35}S) sulfuryl fluoride was rapidly absorbed following a single nose-only inhalation exposure for 4 hours to male F344 rats, with radioactivity detectable in plasma within 30 minutes of exposure to 28 ppm and within 15 minutes of exposure to 247 ppm. By comparing the calculated inhaled dose with the total radioactivity recovered from feces, urine and tissues, it appears as though approximately 12–18% of the inhaled dose was absorbed; however, this estimation is limited by the fact that the recovery potential of the analytical methods used in the metabolism study was not quantified. **Plasma kinetics:** Peak plasma and red blood cell concentrations occurred near the end of the 4-hour exposure period. Clearance from the blood followed a 2-compartment model, with a rapid initial elimination phase (1.1–2.6 hours) followed by a slower elimination phase (56–222 hours) starting approximately 12–24 hours postexposure. The area under the curve was 6–8× larger following exposure to 297 ppm compared to 28 ppm. **Excretion:** Excretion occurred primarily via the urine (86–89% of the total radioactivity excreted) and to a lesser extent the feces (11–14% of the total radioactivity excreted). Elimination via expired air was negligible. Approximately 90% of the radioactivity excreted via the urine and feces was recovered within 24 and 48 hours, respectively, after exposure was terminated. **Distribution/target organs:** The highest levels of radioactivity were detected in the lungs, respiratory and olfactory turbinates, spleen, and kidney. Small amounts of radiolabel were distributed evenly among all tissues within 7 days postexposure, suggesting that ^{35}S was transformed into amino acids and incorporated into tissues. **Metabolism/toxicologically significant compounds:** Sulfate (SO_2) and fluorosulfate (FSO_2) were identified as metabolites in blood and urine. The concentration of FSO_2 in blood was generally 2–3× higher than that of SO_2. Fluoride ion was also detected in urine, plasma, and brain and kidney tissue. Urinary and plasma F concentrations were highest during the exposure period. The concentration of fluoride ion in the urine following exposure to 247 ppm was 8× higher than that following exposure to 28.4 ppm. Concentrations of fluoride ion in brain and kidney tissue were elevated in exposed rats when compared to control rats, but were non-detectable within 8 hours postexposure. **Note:** No repeat exposure study was conducted. Accumulation of sulfuryl fluoride in tissues is not expected given its rapid hydrolysis, but fluoride may accumulate in teeth and bones.

STUDY	SPECIES, STRAIN AND DOSES	LD_{50} or LC_{50}	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
ACUTE STUDIES **TECHNICAL (Sulfuryl Fluoride; SO_2F_2; 99.8%) and END-USE PRODUCT (ProFume; re-pack of the technical grade active ingredient)**			
Oral (1959) Purity not stated	Rat (strain not known), 4 males or 4 females/dose Males: 50, 100, 200 or 400 mg/kg bw Females: 0, 40, 80 or 160 mg/kg bw SO_2F_2 gas bubbled through 1% corn oil solution, administered via gavage	LD_{50} appears to be approximately 100 mg/kg bw	**High toxicity.** Deaths at 160, 200 and 400 mg/kg bw occurred within two hours of dosing. Clinical signs at 80 and 100 mg/kg bw included oily diarrhea and dehydration. Necropsy findings at 80 and 100 mg/kg bw included liver and lung congestion, gastritis, and cloudy swelling in the kidneys. **Unacceptable:** Limited information was provided in the report.
Oral (1959) Purity not stated	Guinea Pig (strain not known), 4 females/dose 0, 50, 100, 200 or 400 mg/kg bw SO_2F_2 gas bubbled through 1% corn oil solution, administered via gavage	LD_{50} appears to be approximately 100 mg/kg bw	**High toxicity.** Deaths at 200 and 400 mg/kg bw occurred within two hours of dosing. Two deaths occurred in the vehicle control group. Clinical signs at 100 mg/kg bw included oily diarrhea and dehydration. Oily diarrhea and loss of hair also noted in vehicle control group. Necropsy findings at 100 mg/kg bw included liver and lung congestion, gastritis, and cloudy swelling in the kidneys. **Unacceptable:** Limited information was provided in the report.
Dermal (1990) 99.67%	Rat, Fischer 344 987 (5 males), 1013 (5 females) or 9599 (5/sex) ppm No control group Rats were exposed with care to prevent inhalation for 4 hours to SO_2F_2 gas; however, LOD of monitoring device was high (20 ppm), and rats may have been exposed via inhalation	LD_{50} > 9599 ppm	**Low toxicity.** No mortality up to analytical concentration of 9599 ppm. Clinical signs noted in most rats included chromodacryorrhea and fecal soiling, persisting for up to 2 days. All animals lost weight up to one day postexposure, but gained weight thereafter. No abnormal necropsy findings (brain, skin and subcutis examined in 9599 ppm exposed rats). **Non-guideline:** Due to nature of test material, traditional dermal toxicity study could not be performed.
Inhalation (1959) Purity not stated	Rat (strain not known), 8–20/dose Target concentrations of 1000, 2000, 4000, 8000 or 15 000 ppm (4.18, 8.35, 16.70, 33.41 or 62.64 mg/L) for 0.1 to 6 hours; analytical concentrations were not provided Exposure conditions were not reported	LC_{50} (target concentration) = 1000 ppm (4.18 mg/L)	**High toxicity.** Deaths occurred at all exposure levels, mostly within 2–3 hours after exposure. Clinical signs included tremors, convulsions, salivation, loss of bladder control, chromodacryorrhea, stiffening to very rigid position followed by toppling over backwards (similar to strychnine poisoning). **Unacceptable:** Limited information was provided in the report.

STUDY	SPECIES, STRAIN AND DOSES	LD_{50} or LC_{50}	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Inhalation (1980) 99.7%	Rat, Fischer 344, 10/sex Males: 0, 450, 1000, 1250, 1425 or 2025 ppm (0, 1.88, 4.18, 5.22, 5.95 or 8.46 mg/L) Females: 0, 320, 450, 700, 790, 1000, 1020, 1200, 1425 or 2025 ppm (0, 1.34, 1.88, 2.92, 3.30, 4.18, 4.26, 5.01, 5.95 or 8.46 mg/L) Whole body exposure, 4 hours	LC_{50} (males) = 1122 ppm (4.69 mg/L) LC_{50} (females) = 991 ppm (4.14 mg/L)	**High toxicity.** Mortalities at 1000 ppm and above occurred during exposure and up to day 6. Clinical signs noted at ≥ 700 ppm and included sedated appearance, prostration, dark/watery eyes, frequent blinking, dark exudate around eyes/mouth/nares, convulsions, moribund appearance, lethargy, bluish tail, little inclination to eat or drink, moving only when forced and wetness in perineal area. Animals recovered from clinical signs within six days after exposure. Decreased body-weight gains were noted at 700 ppm and higher. Increased liver, kidney, testes weights were noted at 450, 1000 and 1250 ppm. Necropsy revealed several lesions in the liver, kidney, spleen, pancreas, lungs, nasal turbinates, stomach, small intestine and heart.
Inhalation (1989) 99.6%	Mouse, B6C3F1, 5/sex/concentration 404, 603 or 1003 ppm (1.69, 2.52 or 4.19 mg/L) Whole body exposure, 4 hours	LC_{50} = 404 to 603 ppm (1.69 to 2.52 mg/L)	**High toxicity.** All animals in the 603 and 1003 ppm groups died by the end of study days 6 and 1, respectively. Clinical signs at 603 ppm included body tremors and lethargy. Body weight loss occurred at 603 ppm on days 1–4. Necropsy revealed decreased ingesta, congestion of the viscera, multifocal erosions/ulcers of the glandular mucosa and distended urinary bladder.
Inhalation (1990) 99.6%	Mouse, CD-1, 5/sex/concentration 596, 692, or 806 ppm (2.49, 2.89 or 3.37 mg/L) Whole body exposure, 4 hours	LC_{50} (males) = 660 ppm (2.76 mg/L) LC_{50} (females) = 642 ppm (2.68 mg/L)	**High toxicity.** Mortalities occurred at 692 and 806 ppm on days 0–8. Clinical signs at 692 and 806 ppm included body tremors and lethargy. Most animals lost weight initially, with recovery by study termination. Necropsy revealed decreased ingesta, congestion of the viscera and decreased amount of fat at 692 and 806 ppm.
Inhalation Published article from 1977	Rat, Sprague-Dawley 5/sex/concentration Exposure concentrations were not identified. Whole body exposure, 1 hour	1-hour LC_{50} (males) = 3730 ppm (15.6 mg/L) 1-hour LC_{50} (females) = 3020 ppm (12.6 mg/L)	**High toxicity.** **Supplemental:** Published article.
Skin Irritation	**Waiver granted.** Cross-reference made to acute dermal toxicity study, where no signs of dermal irritation (skin examined microscopically) were noted.		**Corrosive.** Classification is based on the possibility of cryogenic burns; sulfuryl fluoride causes freezing of skin and eye tissues on contact when released from pressurized steel cylinders. No irritation following exposure to the gas is expected.
Eye Irritation	**Waiver granted.** Rationale: difficult to conduct study due to gaseous form; SO_2F_2 does not pose significant hazard for eye irritation based on human evidence and acute dermal toxicity study.		
Skin Sensitization	**Waiver granted.** Rationale: difficult to conduct study due to gaseous form; SO_2F_2 does not pose significant hazard for skin sensitization based on human evidence.		**Not a dermal sensitizer.** Cryogenic nature of pressurized sulfuryl fluoride will cause irreversible skin damage on contact; therefore, an immune-mediated, sensitization response is not likely to occur. No irritation or sensitization following exposure to the gas is expected.

STUDY	SPECIES, STRAIN AND DOSES[a]	NOAEL and LOAEL	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
SHORT TERM TOXICITY			
66-day dietary (1959) Purity not stated	Rat (strain not known), 10/sex/dose Diet fumigated with SO_2F_2; concentration of SO_2F_2 not determined Concentration of **fluoride** determined to be 0, 19, 53, 350 or 704 ppm Additional 2/sex/dose designated for interim sacrifice at 30 days Fluoride levels determined in the blood, urine (males), kidney, lung, liver, and bone at interim sacrifice	NOAEL and LOAEL could not be determined due to several deficiencies. No effects were noted at 19 ppm fluoride.	**53 ppm fluoride:** ↓ body weight (males: ↓ 10%), dental fluorosis (loss of pigmentation, whiter appearance of teeth) **350 ppm fluoride:** ↓ body weight (males: ↓ 19%), dental fluorosis (darkening and banding of teeth) **704 ppm fluoride:** ↓ body weight (↓ 32%/16% in males/females), dental fluorosis (darkening and banding of teeth), renal glomerular involvement. Dose-dependent ↑ in fluoride content in urine (males; not collected in females) and bone. No effects were noted at interim sacrifice (30 days). **Unacceptable:** Several parameters were not assessed (no eye examination, hemoglobin and total white blood cell examined in female rats, no clinical chemistry, pathology limited to lungs, liver, pancreas, heart, spleen, kidney, testes, adrenals); only limited information was provided in the report.

STUDY	SPECIES, STRAIN AND DOSES [a]	NOAEL and LOAEL	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Two-week inhalation (1985) 99.8%	Rat, Fischer 344 (5/sex/dose) 0, 100, 293 or 597 ppm (0, 100, 293 or 597 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week for 2 weeks; 9 exposures total This study was run concurrently with the 2-week inhalation toxicity study in rabbits.	NOAEL and LOAEL were not established as this is a range-finding study. No adverse effects were noted at 100 ppm (100 mg/kg bw/day).	**100 ppm (100 mg/kg bw/day):** ↑ white blood cell (↑ 25%), ↑ segmented neutrophils (females: ↑ 27%)—non-adverse. **293 ppm (293 mg/kg bw/day):** ↑ white blood cell (↑ 31%/49% in males/females), ↑ segmented neutrophils (females: ↑ 27%), ↑ ALK (males), ↓ albumin (females), ↑ globulin (females), ↑ relative heart and kidney weight (females), ↑ absolute and relative thymus weight (females), slight mineralization of the cornea (females), hyperplasia of the renal collecting ducts, increased basophilia in proximal renal tubules. **597 ppm (597 mg/kg bw/day):** 5/5 males and 4/5 females died or were sacrificed moribund between 2nd and 6th exposures, lethargy, ↓ food consumption, ↓ body weight (males: ↓ 32%), ↓ ingesta in gastrointestinal tract, ↓ size of thymus and lymph nodes, porphyrin staining of face and forelimbs, hyperplasia of renal epithelial papillae, degeneration/regeneration of renal collecting ducts and proximal tubules, necrosis of renal papillae, altered hepatocellular cytoplasmic homogeneity, inflammation of the epicardium, depletion of lymphoid tissue of the spleen and lymph nodes, hypertrophy of the adrenal cortex, mineralization and vacuolation of the adrenal cortex (females), erosion and mineralization of the glandular mucosa of the stomach, hemorrhage of the glandular mucosa of the stomach (females), mineralization of the muscularis of the stomach (males), degeneration of the epididymal ducts and presence of degenerative spermatic elements in the epididymis, edema of the lungs, inflammation of the pleura of the lungs, mineralization of the alveoli, capillary thrombus in the lung, cellular necrosis in the salivary gland, depletion of lymphoid tissues of the thymus, slight mineralization of the cornea (females), cellular necrosis of the olfactory epithelium (males), congestion of multiple organs. **Only surviving female:** body weight loss, ↑ white blood cell (↑ 119%), ↓ lymphocytes, ↑ segmented neutrophils (↑ 180%), ↓ albumin, ↑ globulin, ↑ red blood cell, ↑ hemoglobin, ↑ packed cell volume, ↓ platelets, ↑ blood urea nitrogen, ↑ ALT, ↑ ALK, ↑ glucose, ↓ urinary pH, ↑ urinary glucose, ↑ relative kidney weight., ↓ absolute liver weight, ↓ absolute and relative thymus weight. **Supplemental:** Range-finding study; however, appropriate evaluation of critical endpoints was conducted.

STUDY	SPECIES, STRAIN AND DOSES[a]	NOAEL and LOAEL	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
13-week inhalation (1987) 99.8%	Rat, Fischer 344 (10/sex/dose) 0, 30, 100 or 297 ppm (0, 30, 100 or 297 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week for 13 weeks Fluoride levels measured in blood.	NOAEL = 30 ppm (30 mg/kg bw/day) LOAEL = 100 ppm (100 mg/kg bw/day)	**100 ppm (100 mg/kg bw/day):** dental fluorosis (mottled lower and upper incisors), ↑ segmented neutrophils (females), ↓ absolute brain weight (females). **297 ppm (297 mg/kg bw/day):** ↓ body weight (↓ 5–17%), ↓ body-weight gain (61%/48% of control for males/females), ↑ red blood cell (males), ↑ platelets (males), ↑ segmented neutrophils, ↓ lymphocytes (males), ↑ ALK, ↑ blood urea nitrogen (females), ↓ protein (females), ↓ albumin (females), ↑ globulin (males), ↓ calcium (females), ↑ serum fluoride, ↓ urinary specific gravity (males), dental fluorosis, ↑ relative brain and kidney weight, ↓ absolute brain and liver weight, ↓ absolute thymus weight, ↓ relative liver weight (females), focus in lungs, slight vacuolation in caudate-putamen nuclei, alveolar histiocytosis, inflammation of the nasal mucosa, inflammation of the trachea (males), hyperplasia of renal collecting ducts (females), ↓ protein droplet formation in renal cortex (males).
Two-week inhalation (study report date 2002; conducted in 1988) 99.6%	Mouse, CD-1 (5/sex/dose) 0, 30, 100 or 302 ppm (0, 57, 187 or 567 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week for 2 weeks; 9 exposures total	NOAEL and LOAEL were not established as this is a range-finding study. No effects were noted at 30 ppm (57 mg/kg bw/day).	**100 ppm (187 mg/kg bw/day):** ↑ absolute and relative kidney and liver weight (females), very slight vacuolation of cerebrum and medulla, slight body weight loss (males). **302 ppm (567 mg/kg bw/day):** 5/5 males and 4/5 females died, thin appearance, roughened haircoat, body tremors (males), significant body-weight loss, ↓ ingesta in gastrointestinal tract, ↓ amount of body fat, hepatocellular atrophy secondary to inanition, moderate vacuolation of cerebrum and medulla, erosions and ulcers of the glandular mucosa of the stomach, atrophy of the lacrimal/harderian gland (not examined at lower exposure levels). **Supplemental:** Range-finding study; however, appropriate evaluation of critical endpoints was conducted.
13-week inhalation (1993) 99.6%	Mouse, CD-1 (14/sex/dose) 0, 10, 30 or 100 ppm (0, 19, 56 or 188 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week for 13 weeks Functional operational battery conducted at 4, 8 and 12 weeks Neuropathology and serum fluoride assessed in 4 mice/sex/dose	NOAEL = 30 ppm (56 mg/kg bw/day) LOAEL = 100 ppm (188 mg/kg bw/day)	**30 ppm (56 mg/kg bw/day):** ↑ serum F—non-adverse. **100 ppm (188 mg/kg bw/day):** ↓ body weight (↓ 5–12%), ↓ body-weight gain (38%/65% of control for males/females), ↑ ALK (males), ↑ triglyceride (males), ↑ serum fluoride, very slight vacuolation of brain (caudate-putamen, external capsule of cerebrum and of thalamus/hypothalamus) in main group and in extra neurotoxicity satellite group, hypertrophy of the follicles of the thyroid, ↓ secretory material in salivary gland (males). No exposure-related functional operational battery findings.

STUDY	SPECIES, STRAIN AND DOSES[a]	NOAEL and LOAEL	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Two-week inhalation (1985) 99.8%	Rabbit, New Zealand white (3/sex/dose) 0, 100, 293 or 597 ppm (0, 59, 173 or 352 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week for 2 weeks; 9 exposures total This study was run concurrently with the 2-week inhalation toxicity study in rats.	NOAEL and LOAEL were not established as this is a range-finding study. No adverse effects were noted at 100 ppm (59 mg/kg bw/day).	**100 ppm (59 mg/kg bw/day):** ↑ white blood cell (females: ↑ 42%)—non-adverse. **293 ppm (173 mg/kg bw/day):** ↑ white blood cell (↑ 18%/23% in males/females), ↓ absolute and relative liver weight (males), very slight to moderate cerebral vacuolation and malacia, altered hepatocellular cytoplasmic homogeneity, inflammation of the nasal mucosa, hyperplasia of the spleen (males). **597 ppm (352 mg/kg bw/day):** Convulsions in 1 female after 5th exposure resulting in fractured tibia (this rabbit and another female with fractured vertebrum sacrificed), hyperactivity, body-weight loss, ↑ white blood cell (males: ↑ 66%), ↑ segmented neutrophils (males: ↑ 21%), ↓ lymphocytes (males), ↓ absolute and relative liver weight (males), hyperplasia of lymphoid follicles of the spleen (males), altered cytoplasmic homogeneity of the kidney tubules (females), inflammation of the nasal and tracheal mucosa, collapsed lung (1 males), very slight to moderate cerebral vacuolation and malacia, altered hepatocellular cytoplasmic homogeneity, regeneration/degeneration of the respiratory epithelium (females), thyroid cyst (not assessed at lower doses), hyperplasia of lymph nodes (not assessed at lower doses). **Only surviving female:** ↑ white blood cell (↑ 24%), ↑ segmented neutrophils (↑ 60%), ↓ lymphocytes, ↑ absolute and relative heart weight **Supplemental:** Range-finding study; however, appropriate evaluation of critical endpoints was conducted.
13-week inhalation (1987) 99.8%	Rabbit, New Zealand white (7/sex/dose) 0, 30, 100 or 337 ppm (0, 18, 59 or 199 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week for 13 weeks After 9 exposures, the highest target concentration of 600 ppm was reduced to a target concentration of 300 ppm due to severe toxicity. Fluoride levels measured in blood.	NOAEL = 30 ppm (18 mg/kg bw/day) LOAEL = 100 ppm (59 mg/kg bw/day)	**30 ppm (18 mg/kg bw/day):** ↑ serum F—non-adverse. **100 ppm (59 mg/kg bw/day):**, ↓ body-weight gain (79%/80% of control for males/females), ↑ serum fluoride, ↓ absolute and relative liver weight, moderate cerebral vacuolation (internal and external capsule, putamen, globus pallidus) in 1 female. **337 ppm (199 mg/kg bw/day):** Exposure at 600 ppm for first 9 days resulted in convulsions, head bobbing, rapid breathing, rapid eye blinking, and tremors in 1 male and 1 female, 1 female sacrificed day 10 due to hindlimb paralysis caused by a vertebral fracture, slight ↓ body weight (males), ↓ body-weight gain (60%/73% of control for males/females), ↓ food consumption, ↑ white blood cell, ↑ blood urea nitrogen (females), ↑ ALK, ↑ serum fluoride, ↓ absolute and relative liver weight, degeneration of the nasal olfactory epithelium, hypertrophy and hyperplasia of the respiratory epithelium of the nasal passages as well as brain histopathology: gliosis, hypertrophy of the endothelium, very slight to slight vacuolation or severe malacia of the cerebrum (internal and external capsule, putamen, globus pallidus).

STUDY	SPECIES, STRAIN AND DOSES [a]	NOAEL and LOAEL	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Two-week inhalation (1991) 99.6%	Dog, Beagle (1/sex/dose) 0, 29, 96 or 298 ppm (0, 12, 39 or 122 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week for 2 weeks; 9 exposures total Fluoride levels measured in blood.	NOAEL and LOAEL were not established as this is a range-finding study. Effects were noted at 29 ppm (12 mg/kg bw/day).	**29 ppm (12 mg/kg bw/day):** female lost weight, male showed ↓ body-weight gain. **96 ppm (39 mg/kg bw/day):** female gained weight, male lost weight, ↑ serum fluoride. **298 ppm (122 mg/kg bw/day):** tremors and tetany between 5th and 9th exposures in both dogs, both dogs lost weight, ↑ serum fluoride, female had exudate in lumen of nasal tissues and subacute inflammation of the tracheal mucosa, increased severity (slight) of inflammation of the respiratory epithelium in both dogs. **Supplemental:** Range-finding study; however, appropriate evaluation of critical endpoints was conducted.
13-week inhalation (1992) 96.26% minimum	Dog, Beagle (4/sex/dose) 0, 30, 99 or 198 ppm (0, 12, 41 or 81 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week for 13 weeks	NOAEL = 99 ppm (41 mg/kg bw/day) LOAEL = 198 ppm (81 mg/kg bw/day)	**99 ppm (41 mg/kg bw/day):** ↓ body-weight gain (males: 72% of control) - non-adverse. **198 ppm (81 mg/kg bw/day):** clinical signs (lateral recumbency, tetany, tremors, salivation, incoordination, ↓ activity) in 1 male shortly after exposure on day 19, slight ↓ body weight (males: ↓ 9–11%), ↓ body-weight gain (66%/77% of control for males/females), ↑ relative brain and lung weight (males), very slight gliosis and vacuolation of the midbrain in 1 male that also displayed tremors and tetany and in one female.

STUDY	SPECIES, STRAIN AND DOSES [a]	NOAEL and LOAEL	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
One-year inhalation (1993) 99.8%	Dog, Beagle (4/sex/dose) 0, 21, 79 or 198 ppm (0, 9, 32 or 81 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week for 52 weeks Animals in the 197 ppm group were removed after 9 months due to deaths and moribundity.	NOAEL = 21 ppm (9 mg/kg bw/day) LOAEL = 79 ppm (32 mg/kg bw/day)	**79 ppm (32 mg/kg bw/day):** ↓ body-weight gain (females: 74% of control), ↑ absolute and relative lung weight (females), ↓ absolute and relative liver weight (females), alveolar inflammation (1 female), dental fluorosis, aggregates of alveolar macrophages, transient hematology and clinical chemistry findings (non-adverse): ↑ platelets at 6 months, ↑ white blood cell (males) at 6 months, ↑ segmented neutrophils (males) at 9 months, ↓ lymphocytes (males) at 9 months, ↑ triglycerides (males) at 9 months, ↑ phosphorus (females) at 6 months. **198 ppm (81 mg/kg bw/day):** at approximately 9 months: 1 male and 3 females sacrificed moribund, 1 male died, remaining animals removed from study; rapid, noisy and shallow breathing in 1 male and 2 females shortly before removal from the study, ↓ activity in 1 male and 3 females appeared thin shortly before removal, body-weight loss week 1, ↓ body-weight gain (44%/31% of control for males/females), ↑ platelets, ↑ white blood cell, ↑ segmented neutrophils, ↓ lymphocytes, ↓ albumin, ↑ globulin, ↑ CK, ↑ blood urea nitrogen (males), ↑ cholesterol, ↑ triglycerides, ↑ phosphorus, ↓ calcium (females), ↑ potassium (females), ↑ ALK (females), ↓ glucose (females), ↓ ingesta, consolidation of lungs, myeloid hyperplasia of bone marrow, inflammation of the nasal respiratory epithelium (females), inflammation of the interstitium of the pancreas, inflammation of the cerebellar ependyma (males), malacia of the caudate nucleus, dilation of the renal tubules with proteinaceous casts (males), hepatocellular atrophy secondary to inanition, alveolar inflammation, atrophy of lymphoid tissues, inflammation and plasmacytosis of lymphoid tissues (females), hypertrophy of epithelial cells of the thyroid gland, dental fluorosis. Organ weight data not available due to early removal.

STUDY	SPECIES, STRAIN AND DOSES[a]	NOAEL and LOAEL	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
CHRONIC TOXICITY AND ONCOGENICITY			
18-month inhalation—oncogenicity (1993) 99.8%	Mouse, CD-1 (50/sex/dose) 0, 5, 20 or 80 ppm (0, 10, 38 or 150 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week for 18 months Additional 10 rats/sex/dose for interim sacrifice at 12 months This study was run concurrently with the 2-year study in rats.	NOAEL = 20 ppm (38 mg/kg bw/day) LOAEL = 80 ppm (150 mg/kg bw/day)	**80 ppm (150 mg/kg bw/day):** ↑ mortality (females > males), ↓ body weight (↓ 3–15%) and body-weight gain (↓ 32–35%). **Interim sacrifice:** very slight vacuolation of caudate-putamen (1 male), vacuolation of external capsule of brain, hypertrophy of epithelial cells of the thyroid gland. **Final sacrifice:** very slight vacuolation of external capsule of the brain, impacted esophagus with feed in lumen (males), thrombus of heart (females), hyperplasia of epithelial cells of the larynx (females), congestion of the lungs (females), suppurative lumen of nasal tissues (males), atrophy of the spleen (females) and thymus, hypertrophy of epithelial cells of the thyroid gland (males), hyperplasia in the trachea, ↑ amyloidosis (females: jejunum, renal glomerulus, parathyroid interstitium; renal amyloidosis reported to be major cause of death. **Not oncogenic**

STUDY	SPECIES, STRAIN AND DOSES[a]	NOAEL and LOAEL	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Two-year inhalation—combined chronic toxicity/oncogenicity (1993) 93.6–99.7%	Rat, Fischer 344 (50/sex/dose) 0, 5, 20 or 80 ppm (0, 5, 20 or 80 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week for 2 years Additional 15 rats/sex/dose for interim sacrifice at 1 year; also used for assessment of chronic neurotoxicity (results below) This study was run concurrently with the 18-month mouse study.	NOAEL = 5 ppm (5 mg/kg bw/day) LOAEL = 20 ppm (20 mg/kg bw/day)	**5 ppm (5 mg/kg bw/day):** slight ↓ body-weight gain 12–18 months (82% of control)—non-adverse. **20 ppm (20 mg/kg bw/day):** ↓ body-weight gain 12–18 months (70%/78% of control for males/females), ↑ white blood cell (males), ↑ segmented neutrophils (females), ↓ lymphocytes, slight ↑ blood urea nitrogen at 19 months (females), dental fluorosis (mottled incisors), pale foci in the lungs at terminal sacrifice (males: 0, 1, 8, 46; females: 0, 0, 1, 46). **80 ppm (80 mg/kg bw/day):** all rats died or sacrificed moribund, cause of death in most cases was advanced chronic renal disease, ↑ deaths noted after 18 months for males and 20 months for females; ↓ body weight starting at 17 months, ↓ body-weight gain (males 89% of control 6-18 months; females 11% of control 12-18 months), body-weight loss 12–18 months (males), ↑ white blood cell, ↑ platelets, ↑ segmented neutrophils, ↓ lymphocytes, ↑ blood urea nitrogen, ↓ total protein, ↓ albumin, ↑ cholesterol, ↑ triglycerides, ↑ creatinine, ↑ serum phosphorus, ↓ serum chlorine, ↑ urinary blood, ↑ urinary specific gravity and protein at 6 and 12 months (females), ↓ urinary specific gravity at 19 and 21 months, ↑ absolute and relative liver and kidney weight (males, interim sac), dental fluorosis (mottled incisors), mineralization of several tissues, histopathology in other organs (heart, stomach, adrenal, thyroid, liver, spleen, lymph nodes, cornea, parathyroid), several effects secondary to renal disease, renal lesions (glomerulonephropathy, pale kidneys, roughened surface of kidneys), respiratory tract lesions (foci in lungs, multifocal aggregates of alveolar macrophages, hyperplasia and inflammation of the respiratory epithelium lining the nasal passages, congestion of the lungs (females), inflammation of the trachea and larynx), very slight vacuolation of the cerebral cortex and thalamus/hypothalamus (males). **Incidence of dental fluorosis:** Very slight— Interim sacrifice males: 0, 0, 3, 3; females: 0, 0, 0, 9 Final sacrifice: males: 0, 0, 10, 12; females: 0, 0, 2, 4 Slight— Interim sacrifice: males: 0, 0, 0, 7; females: 0, 0, 0, 0 Final sacrifice: males: 0, 0, 0, 38; females: 0, 0, 0, 46 **Not oncogenic**

STUDY	SPECIES, STRAIN AND DOSES[a]	NOAEL and LOAEL	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY			
Two-generation reproduction—inhalation (1992) 93.6-98.8%	Rat, Sprague-Dawley (30/sex/dose) **P:** 0, 5, 21 or 149 ppm (0, 5, 21 or 149 mg/kg bw/day) **F_1:** 0, 5, 20 or 150 ppm (0, 5, 20 or 150 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week prior to mating; 6 hours/day, 7 days/week during mating, gestation and lactation. Maternal animals were not exposed from GD 20 to PND 4. From LD 5 to 21, pups remained in nesting cages while dams were placed in exposure chambers for 6 hours.	Parental NOAEL = 5 ppm (5 mg/kg bw/day) Parental LOAEL = 20 ppm (20 mg/kg bw/day) Reproductive NOAEL = ≥ 149 ppm (149 mg/kg bw/day) Reproductive LOAEL could not be determined Offspring NOAEL = 20 ppm (20 mg/kg bw/day) Offspring LOAEL = 149 ppm (149 mg/kg bw/day)	**P Parental Effects** **21 ppm (21 mg/kg bw/day):** ↓ body-weight gain week 1 (females: ↓ 11%), foci in lungs (males), aggregates of alveolar macrophages. **149 ppm (149 mg/kg bw/day):** clinical signs (males: chromodacryorrhea, malocclusion, rough haircoat, thin appearance), ↓ body weight (males: ↓ 6-9%), ↓ body-weight gain (males: ↓ 14%), ↓ body-weight gain week 1 (females: ↓ 10%), ↓ body-weight gain weeks 1–10 premating (females: ↓ 9%), ↓ body weight GD 21 (↓ 7%) and LD 1, 4, and 7 (↓ 11–12%), ↓ body-weight gain GD 1–21 (↓ 16%), ↓ body-weight gain LD 1–4 (↓ 77%), ↑ total body-weight gain during lactation (↑ 161%), ↑ total body-weight gain during exposure LD 4–21 (↑ 312%) foci in lungs, very slight to slight vacuolation of caudate-putamen (males: 0, 0, 0, 11; females: 0, 0, 0, 14), inflammation of lungs, aggregates of alveolar macrophages, dental fluorosis (dark teeth), dental abnormalities (males: overgrown lower incisors, malformed, worn or broken upper incisors). **F_1 Parental Effects** **20 ppm (0.09 mg/L; 20 mg/kg bw/day):** ↓ body-weight gain week 1 (females: ↓ 29%), foci in lungs, aggregates of alveolar macrophages. **149 ppm (0.62 mg/L; 149 mg/kg bw/day):** ↓ body weight (males: ↓ 11–14%), ↓ body-weight gain (males: ↓ 30% week 1, ↓ 10% weeks 1–20), ↓ body weight weeks 1-12 premating (females: ↓ 8–12%), ↓ body-weight gain week 1 (females: ↓ 31%), ↓ body weight GD 1–21 (↓ 7–9%), ↓ body weight LD 1–21 (↓ 5–10%), ↑ body-weight gain during exposure LD 4–21 (↑ 78%), foci in lungs, dental fluorosis (dark teeth), very slight to slight vacuolation of caudate-putamen (males: 0, 0, 0, 2; females: 0, 0, 0, 7), inflammation of the lungs, aggregates of alveolar macrophages. **F_1 Offspring Effects** **21 ppm (0.09 mg/L; 20 mg/kg bw/day):** stomach void of milk upon clinical examination (incidence: pups 2, 0, 6, 15; litter 2, 0, 1, 3). **149 ppm (0.62 mg/L; 149 mg/kg bw/day):** ↓ body weight LD 4–21 (↓ 14–18%), stomach void of milk. **F_2 Offspring Effects** **20 ppm (0.09 m/L; 20 mg/kg bw/day):** stomach void of milk upon clinical examination (incidence: pups 1, 0, 25, 36; litter 1, 0, 3, 4). **150 ppm (0.63 mg/L; 150 mg/kg bw/day):** ↓ body weight LD 7–21 (↓ 8–12%), females affected slightly more than males; stomach void of milk upon clinical examination. **Reproductive Effects** No effects were noted.

STUDY	SPECIES, STRAIN AND DOSES[a]	NOAEL and LOAEL	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Developmental toxicity—inhalation (1981) 99.8%	Rat, Fischer 344 (29–32 females/dose) 0, 25, 76 or 225 ppm (0, 25, 76 or 225 mg/kg bw/day) Whole body exposure, 6 hours/day from GD 6 to 15	Maternal NOAEL = 76 ppm (76 mg/kg bw/day) Maternal LOAEL = 225 ppm (225 mg/kg bw/day) Developmental NOAEL ≥ 225 ppm (225 mg/kg bw/day) Developmental LOAEL could not be determined	**Maternal Toxicity** **225 ppm (225 mg/kg bw/day):** ↓ body-weight gain GD 6–8 (↓ 57%), ↓ body-weight gain GD 9–15 (↓ 8–9%), ↑ water consumption. **Developmental Toxicity** No developmental effects were noted. **No evidence of teratogenicity or increased sensitivity of the young.**
Developmental toxicity—inhalation (1981) 99.8%	Rabbit, New Zealand white (21–26 females/dose) 0, 25, 76 or 225 ppm (0, 15, 45 or 133 mg/kg bw/day) Whole body exposure, 6 hours/day from GD 6 to 18	Maternal NOAEL = 76 ppm (45 mg/kg bw/day) Maternal LOAEL = 225 ppm (133 mg/kg bw/day) Developmental NOAEL = 76 ppm (45 mg/kg bw/day) Developmental LOAEL = 225 ppm (133 mg/kg bw/day)	**Maternal Toxicity** **225 ppm (133 mg/kg bw/day):** ↓ body weight GD 29 (↓ 7%), body weight loss GD 9–18 and 19–28. **Developmental Toxicity** **225 ppm (133 mg/kg bw/day):** ↓ mean fetal weight (↓ 14%), pale liver. **No evidence of teratogenicity or increased sensitivity of the young.**
NEUROTOXICITY			
Acute neurotoxicity—inhalation (1993) 99.8%	Rat, Fischer 344 (12 females/dose) 0, 97 or 291 ppm (0, 93 or 291 mg/kg bw/day) Whole body exposure, 6 hours/day for 2 days Functional operational battery, grip performance, landing foot splay, motor activity, electrodiagnostic responses (flash evoked potential, auditory brainstem response, somatosensory evoked potential) were examined within 24 hours after the last exposure.	NOAEL ≥ 291 ppm (291 mg/kg bw/day) LOAEL could not be determined	No exposure-related effects. **Note:** The USEPA reviewed and accepted the procedure prior to conduct. Only females were used in this study; females are more sensitive than males to effects on flash evoked potentials in the subchronic neurotoxicity study. Neuropathology was not assessed as evoked potentials were a more sensitive neurotoxicity endpoint than neuropathology in the subchronic neurotoxicity study.

STUDY	SPECIES, STRAIN AND DOSES[a]	NOAEL and LOAEL	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Subchronic neurotoxicity—inhalation (1986) 99.8%	Rat, Fischer 344 (7/sex/dose) 0, 30, 100 or 297 ppm (0, 30, 100 or 297 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week for 13 weeks 2 rats/sex from the 0 and 297 ppm groups retained for a recovery period of 2 months following last exposure and evaluated for auditory brainstem response and histopathology.	NOAEL and LOAEL could not be determined due to several deficiencies. No effects noted at 30 ppm (30 mg/kg bw/day).	**100 ppm (100 mg/kg bw/day):** lacrimation (males), slowed waveforms for somatosensory and visual evoked potentials (females), slowed auditory brainstem response (males), foci in lungs, dental fluorosis (mottled lower and upper incisors). **297 ppm (297 mg/kg bw/day):** ↓ body weight (8–22%), ↓ body-weight gain (males: ↓ 66%), body-weight loss (females), lacrimation, unkempt fur, slowed waveforms (visual evoked potential, somatosensory evoked potential, caudal nerve action potential, auditory brainstem response), ↓ cortical flicker fusion, ↓ core body temperature, foci in lungs, dental fluorosis (mottled lower and upper incisors), vacuolation of the caudate-putamen. No effects on histopathology or auditory brainstem response after 2-month recovery period. **Unacceptable:** Several functional operational battery parameters and motor activity were not assessed, no positive control data; however, the results of this study were considered in conjunction with the results of the neurotoxicity phase of the 2-year rat study (see below).
One-year neurotoxicity—inhalation (1994) 93.6-99.7%	Rat, Fischer 344 (15/sex/dose) 0, 5, 20 or 80 ppm (0, 5, 20 or 80 mg/kg bw/day) Whole body exposure, 6 hours/day, 5 days/week for 1 year Neuropathology assessed in 5 rats/sex/dose Rats were a satellite group in the 2-year combined chronic toxicity/oncogenicity study	**Neurotoxicity** NOAEL = 80 ppm (80 mg/kg bw/day) LOAEL not determined **Systemic toxicity** NOAEL = 20 ppm (20 mg/kg bw/day) LOAEL = 80 ppm (80 mg/kg bw/day)	**80 ppm (80 mg/kg bw/day):** very slight focus in the lungs (2/5 males, 1/5 females); no neuropathology observed.
Developmental neurotoxicity	Waiver rationale was submitted with the following arguments: no chronic dietary exposure to SO_2F_2 is expected, minimal potential for inhalation exposure, metabolism studies indicate a lack of systemic exposure to SO_2F_2, concerns regarding animal welfare, and potentially confounded scientific/technical aspects of an inhalation developmental neurotoxicity. This waiver request was unacceptable.		

GENOTOXICITY

STUDY	SPECIES and STRAIN or CELL TYPE AND CONCENTRATIONS or DOSES	RESULTS
Gene mutations in bacteria (1990) 99.6%	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 0, 300, 1000, 3000, 10 000 or 30 000 ppm in air with and without metabolic activation	**Negative.** Cytotoxicity at 30 000 ppm. No dose-dependent or reproducible increase in revertant frequency.
Gene mutations in bacteria (2002) 99.8%	*E. Coli* WP2uvrA 0, 100, 300, 1000, 3000, 10 000, 30 000 or 50 000 ppm in air with and without metabolic activation.	**Negative.** Cytotoxicity at 50 000 ppm. No increase in mean revertant colonies/plate over background.

STUDY	SPECIES and STRAIN or CELL TYPE AND CONCENTRATIONS or DOSES	RESULTS
Gene mutations in mammalian cells in vitro (2002) 99.8%	Mouse lymphoma L5178Y cells (TK locus) 0, 100, 500, 1000, 2000, 2500, 3000, 3500, 4000, 5000 or 6000 ppm in air with and without metabolic activation.	**Positive.** Increases in genetic mutations were noted at 2000 and 2500 ppm in the presence of metabolic activation and at 2500, 3000 and 3500 ppm in the absence of metabolic activation in one assay. Cytotoxicity was demonstrated at 4000 ppm and above in the presence of metabolic activation and at 3500 ppm and above without metabolic activation.
Chromosome aberrations in vitro (2002) 99.8%	Lymphocytes from male Crl:CD BR Sprague-Dawley rats 0, 100, 500, 1000, 2500, 5000, 10 000, 15 000, 20 000, 25 000, 30 000, 35 000, 38 000, 40 000 or 50 000 ppm in air with or without metabolic activation.	**Positive** for chromosomal aberrations at 10 000 ppm and above in the absence of metabolic activation and at 15,000 ppm and above in the presence of metabolic activation. Cytotoxicity was demonstrated at 30 000 ppm and above in the presence and absence of metabolic activation.
Unscheduled DNA synthesis in vitro (1991) 97.4%	Primary rat hepatocytes (male SD rats) 0, 102, 204, 408, 612, 816, 1020 or 1530 ppm in air	**Negative.** Cytotoxicity at 1530 ppm. No increase in nuclear silver grain counts over control.
Micronucleus assay in vivo—inhalation (1990) 99.6%	Male and female CD-1 (ICR) mice (5/sex/dose/sampling time) 0, 50, 175 or 520 ppm (0, 33, 117 or 347 mg/kg bw) Single 4-hour inhalation exposure, whole body; bone marrow harvested 24, 48 and 72 hours postexposure	**Negative.** Cytotoxicity was demonstrated in males exposed to 175 ppm (117 mg/kg bw). Two female mice exposed to 520 ppm (347 mg/kg bw) died.

SPECIAL STUDIES		
STUDY	**SPECIES, STRAIN AND DOSES**	**RESULTS**
Induced incapacitation—inhalation (1986) 99.8%	Rat, Fischer 344 (5 males/dose) Target concentrations of 4000, 10 000, 20 000 or 40 000 ppm; analytical concentrations were not provided. Whole body exposure until rats became incapacitated. Time to incapacitation measured. Designed to determine how long a person might have 'functional coordination' or 'escape capability' during exposure to high levels of SO_2F_2.	**4000 ppm:** incapacitation within 42 minutes of exposure, all rats died within 2.5 hours postexposure. **10 000 ppm:** incapacitation within 16 minutes of exposure, ↑ salivation, red-stained lacrimation, cyanosis (reversible after exposure was terminated), all rats died within 1 hour postexposure, mottled lung, fluid-filled trachea, alveolar edema, alveolar hemorrhage. **20 000 ppm:** incapacitation within 10 minutes of exposure, ↑ salivation, red-stained lacrimation, cyanosis (reversible after exposure was terminated), all rats died within 10 minutes postexposure, failure of lungs to collapse, mottled lungs, fluid-filled trachea, alveolar edema, edema of interstitium of the lung, alveolar hemorrhage. **40 000 ppm:** incapacitation within 6 minutes of exposure, ↑ salivation, red-stained lacrimation, cyanosis (reversible after exposure was terminated), all rats died within 10 minutes postexposure, failure of lungs to collapse, mottled lungs, fluid-filled trachea, alveolar edema, edema of interstitium of the lung. **Effects at all concentrations:** mild diarrhea, convulsions, liver congestion, congestion of blood vessels in the lung, edema and/or hemorrhage of the interstitium of the lung. Respiration stopped for 15–30 seconds after convulsions. **Supplemental:** Non-guideline.

STUDY	SPECIES, STRAIN AND DOSES	RESULTS
Effects of treatment with calcium gluconate or anticonvulsants—inhalation (1985) 99.8%	Rat, Fischer 344 (5 males/dose) **Calcium gluconate Study** Target concentrations of 0, 4000 or 10 000 ppm, exposed for 55, 45 or 16 minutes, respectively. Calcium gluconate (therapeutic treatment for fluoride ion toxicity) administered via i.p. injection either before or after exposure. **Anticonvulsant Study** Target concentrations of 4000 or 10 000 ppm, exposed until incapacitated. Anticonvulsant (phenobarbital, diphenylhydantoin, or diazepam) administered via i.p. injection either before or after exposure. Whole body exposures; analytical exposure concentrations not provided.	**Calcium Gluconate Study** **Pre-exposure treatment:** ↑ survival in rats exposed to 4000 ppm SO_2F_2, but surviving animals were extremely debilitated and exhibited convulsions. **Postexposure treatment:** all rats died within 3 days postexposure; no protection against mortality. ↑ serum calcium in rats treated with CaG; ↑ serum fluoride and ChE, ↓ serum Mg in rats exposed to SO_2F_2. **Anticonvulsant Study** **Phenobarbital—pre-exposure treatment:** no convulsions during exposure, no convulsions for 3 days postexposure. **Phenobarbital—postexposure treatment:** severity of convulsions lessened compared to rats exposed to SO_2F_2 receiving no anticonvulsant. **Diphenylhydantoin—pre-exposure treatment:** no convulsions during exposure, longer and more severe convulsions after exposure compared to rats exposed to SO_2F_2 receiving no anticonvulsant, no further testing with this anticonvulsant. **Diazepam—pre-exposure treatment:** no convulsions during exposure, similar convulsive activity as seen in rats exposed to SO_2F_2 receiving no anticonvulsant—additional doses afer exposure resulted in milder and shorter convulsions. **Diazepam—postexposure treatment:** similar convulsive activity as seen in rats exposed to SO_2F_2 receiving no anticonvulsant. **Supplemental:** Non-guideline.
Ultrastructural assessment of lungs—inhalation (1987) 99.8%	Rat, Fischer 344 (2-3 males/dose) Target concentrations of 0, 4000 or 20 000 ppm; analytical concentrations were not provided Whole body exposure until rats became incapacitated. Lungs assessed by electron microscopy.	**4000 ppm:** incapacitation within 43 minutes, moribundity within 83 minutes; congestion, edema and hemorrhage of the lungs; cellular swelling and focal protrusions in Type I epithelial cells; edema, red blood cells and fibrin present in alveoli and interstitial spaces. **20 000 ppm:** Incapacitation within 13 minutes, moribundity within 31 minutes, congestion, edema and hemorrhage of the lungs (more extensive than at 4000 ppm); cellular swelling and focal protrusions in Type I epithelial cells; edema, red blood cells and fibrin present in alveoli and interstitial spaces; swelling of endothelial cells and Type II epithelial cells, multifocal destruction of the alveolar wall, thrombosis. Changes to cellular structure of lungs following inhalation of high concentrations of sulfuryl fluoride are probably not a direct cause of death as animals exposed to 4000 ppm became moribund in the absence of significant pulmonary injury. **Supplemental:** Non-guideline.

STUDY	SPECIES, STRAIN AND DOSES	RESULTS
Effect of acute exposure on selected physiological parameters—inhalation (1985) 99.8%	Rat, Fischer 344 (1–3/sex/dose) Target concentrations of 4000 or 20 000 ppm; analytical concentrations were not provided. Head only exposure until the rats died. Body temperature, blood pressure, heart rate, ECG and EEG measured.	**4000 ppm:** pale ears and extremities, death within 65 to 90 minutes, ↓ body temperature (7°C in 80 minutes), ↑ blood and pulse pressure, ↓ heart rate, ↓ respiratory rate, pale lungs, congestion of lung with perivascular and alveolar edema (only 1 rat examined microscopically). **20 000 ppm:** pale ears and extremities, death within 9 to 19 minutes, body temperature not recorded due to short survival time, ↑ blood and pulse pressure, ↓ heart rate, ↓ respiratory rate, pale lungs. Just prior to death at 20 000 ppm: ↑ blood pressure and heart rate, ↑ pulse pressure, laboured and irregular breathing, power loss and spikes in EEG, simultaneous cessation of all physiological parameters. Controlling body temperature did not appear to increase survival time. Bursts of electrical activity in the brain often associated with a seizure noted in some rats close to death. No convulsions were observed. No slowing of the brain electrical activity characteristic of an anaesthetic effect was noted. Study authors concluded that death may be associated in some manner with the blocking of the endogenous energy-producing process of oxidative phosphorylation in glycolysis. **Supplemental:** Non-guideline.
Effects of acute exposure on respiration— inhalation (1983) 99.8%	Rat, Fischer 344 (4 males/dose) Target concentrations of 0, 4000 or 10 000 ppm; analytical concentrations were not provided. Head only exposure for 20 minutes. Respiratory frequency, tidal volume and minute volume were measured.	**4000 ppm:** ↑ in respiratory frequency (39%) , ↓ in tidal (30%) and minute (23%) volumes (peak changes after 2 minutes of exposure); values returned to pre-exposure levels after 10 minutes of exposure. **10 000 ppm:** ↑ in respiratory frequency (60%), ↓ in tidal (59%) and minute (53%) volumes, rats appeared ill after 20 minutes of exposure. Effects typical of a pulmonary irritant as opposed to a sensory irritant. **Supplemental:** Non-guideline.

STUDY	SPECIES, STRAIN AND DOSES	RESULTS
Neurobehavioural evaluation of methyl bromide and sulfuryl fluoride fumigators (1986) Published article	Human (18–32 males/group) Groups consisted of fumigators exposed to methyl bromide, fumigators exposed to sulfuryl fluoride, fumigators exposed to both methyl bromide and sulfuryl fluoride, and a reference group with no direct exposure to fumigants on a regular basis. Medical/symptom questionnaire and clinical neurological examination, nerve conduction and neurobehavioural tests administered.	Fumigators working with sulfuryl fluoride showed impaired neurological function in the following areas: General symptoms— muscle aching and fatigue, coordination problems, slurred speech, depression, stumbling when walking, dizziness, weaving and staggering. Lower extremity motor/sensory activity—unable to walk on heels or toes, tingling and numbness in feet Upper extremity motor/sensory activity— muscle weakness in hands, slow/clumsy fingers/thumbs, tremors when arm held out with eyes closed, absent/clonic biceps reflex, problems touching finger to nose, tingling and numbness in hands. Vision problems—blurred vision, focus problems, eye twitches, required to wear corrective lenses. Cognitive function - impaired memory, association, tracing ability. Fumigators exposed to methyl bromide exhibited symptoms with increased incidence and severity when compared to fumigators working with sulfuryl fluoride. **Supplemental:** Human study.
Compound-induced Mortality: Most rats and mice exposed to 597 ppm and 302 ppm, respectively, died during the 2-week inhalation toxicity studies. All animals exposed to 198 ppm in the 1-year dog study were sacrificed moribund within 9 months of exposure. Increased mortality was noted in the 18-month oncogenicity study in the mouse at 80 ppm; amyloidosis caused of many of these deaths. In the 2-year combined chronic toxicity/oncogenicity study in the rat, all animals exposed to 80 ppm died or were sacrificed moribund; advanced chronic renal disease was determined to be the cause of many of these deaths. Two mice in the micronucleus study died after exposure to 520 ppm sulfuryl fluoride.		

Conversions

For studies conducted via the inhalation route, doses in ppm were converted mg/L (acute studies only) and a daily dose (mg/kg bw/day) inhaled by the test animals (repeated exposure studies) using the following formulas:

$mg/L = ppm\ (m^3/10^6\ m^3) \times molecular\ weight\ (102.1\ g/mol) \div 24.45\ L\ air/mol\ gas\ (at\ 25°C\ and\ 101.3\ kPa) \times 10^3\ mg/g$

$$\text{Inhaled dose (mg/kg bw/day)} = \text{concentration (ppm)} \times 4.17\ mg/m^3 \times \text{respiration rate } (m^3/\text{kg bw/day}) \times \frac{\text{hours exposed}}{24\ \text{hours/day}}$$

The value of 4.17 mg/m^3 is used to convert the dose in ppm to mg/m^3 and is based on the molecular weight of sulfuryl fluoride (102.1 g/mol) and the molar volume of gas (24.45 L/mol). The animal respiration rate is equal to 0.96 m^3/kg bw/day for rats, 1.80 m^3/kg bw/day for mice, 0.57 m^3/kg bw/day for rabbits, and 0.39 m^3/kg bw/day for dogs (Cal-DPR 2005a). The animal respiration rate is divided by 24 hours to convert a daily inhalation rate to an hourly inhalation rate, and then multiplied by the hours that the animals were exposed to determine the inhaled dose during the exposure period.

The respiration rates used by the California Department of Pesticide Regulation were selected for the review of sulfuryl fluoride because values were provided for all test species and were not significantly different from those currently used by the PMRA. There were some differences between respiration rates normally used by the PMRA with those used by other agencies. Most notably, the rabbit respiration rate used by the USEPA (0.38 m^3/kg bw/day) was apparently based on an allometric equation of inhalation rate in m^3/day = 0.46 body weight $^{0.8307}$ and a body weight of 3 kg from a 1988 USEPA Document (USEPA 1988). According to the California Department of Pesticide Regulation, that value is no longer valid, and the USEPA currently uses mean inhalation rates of 0.55 m^3/kg bw/day and 0.52 m^3/kg bw/day, respectively, for male and female rabbits (USEPA 1994). These values are similar to the Department of Pesticide Regulation value of 0.54 m^3/kg bw/day (Cal-DPR 2005a).

Appendix II Environmental Assessment

Table 1 Chemical and Physical Properties of Sulfuryl Fluoride

Parameter	Value	Comment
Chemical structure		SO_2F_2
Water solubility at 20°C	750 or 1040 mg/L	Very soluble
Boiling point	-55°C	A gas at environmentally relevant temperatures
Vapour density	3.52 (air = 1)	
Vapour pressure	1.6×10^6 Pa	Very high volatility (Kennedy and Talbert 1977)
Henry's law constant (1/H)	1.1–1.5	Rapid loss from a water surface or moist soil (USEPA 1975a)
log K_{ow}	0.41	Bioconcentration is unlikely (USEPA 1975b)
UV absorption	No absorption at $\lambda > 300$ nm	Low potential for phototransformation

Table 2 Risk Characterization

Risk Quotient (RQ)	Risk Category
< 0.1	Negligible risk
≥ 0.1 to < 1	Low risk
≥ 1 to < 10	Moderate risk
≥ 10 to < 100	High risk
≥ 100 to < 1000	Very high risk
≥ 1000	Extremely high risk

Table 3 Summary of Mammalian and Avian Risk

Exposure Scenario[1]	Inhalation Endpoint	Risk Quotient	Comments
Target fumigation concentration (1.28×10^8 µg/m^3; 30 702 ppm)	Rat = 4.14×10^5 µg/m^3 (99.1 ppm) Mouse = 1.69×10^5 µg/m^3 (50.2 ppm) Bird = 0.2×10^5 µg/m^3 (4.8 ppm)	Rat = 309 Mouse = 757 Bird = 6400	These concentrations are not expected to be found in the environment. Therefore, a refined EEC in air was determined. (See below)
Maximum monitoring concentration during fumigation (85451.1 µg/m^3; 20.5 ppm)		Rat = 0.2 Mouse = 0.5 Bird = 4.25	Low risk to small mammals and a moderate risk to birds.
95% of monitoring concentrations during fumigation (27143.07 µg/m^3; 6.5 ppm)		Rat = 0.07 Mouse = 0.2 Bird = 1.4	Low to negligible risk to small mammals and moderate risk to birds.
Modelling data fumigation (draft result 3.19×10^5 µg/m^3; 77 ppm)		Rat = 0.8 Mouse = 1.9 Bird = 14.5	Low to moderate risk to small mammals and a high risk to birds.

[1] Maximum monitoring and modelling data are from 5 m from a mill

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